REPORT NUMBER 17

Transplantation of Allogeneic Hematopoietic Stem Cells from Unrelated Donors in Adult Patients at the MUHC

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Report available at www.mcgill.ca/tau/

Final Version April 20th, 2005 (Revised: 25/SEP/2006)

Invitation.

This document was designed to assist decision-making in the McGill University Health Centre. Others are welcome to make use of it with acknowledgment.

Foreword

In June 2004, the Technology Assessment Unit (TAU) of the McGill University Health Centre (MUHC) received a request from the Administrative Director for Medicine, Surgery, and Women's Health, Mr.Gary Stoopler, to evaluate the use of umbilical cord blood as an alternative source for hematopoietic stem cell transplantation.

There are two issues that underlie this request. The first is whether the MUHC should expand stem cell transplantation through the use of cord blood. The transplantation of stem cells derived from the bone marrow or peripheral blood of HLA matched donors is already an accepted therapeutic technique that is in use at the MUHC. However, suitable cells can often not be found, or found sufficiently rapidly to be used in the restricted time interval available to each patient. When this occurs the use of cord blood offers a possible solution.

The second issue is whether the health benefits of stem cell transplantation, whatever the source of cells, is sufficiently great to justify its extension to an increased number of cases. The transplantation of stem cells from the bone marrow or cord blood of unrelated donors is already limited at the MUHC because of lack of resources. If no new funds become available for this procedure, should its expansion be authorized at the MUHC at the expense of the existing budget?

Clarification

In order to improve the clarity of the text of this report, whenever stem cell transplantation is mentioned, unless otherwise specified, we are referring to hematopoietic stem cell transplantations from any of the three potential sources: bone marrow, peripheral blood, or cord blood.

Executive Summary

- Hematopoietic stem cell transplantation from both related and unrelated donors is an accepted treatment option for patients with life-threatening malignant and non-malignant hematologic disorders. It constitutes the only available treatment for some hematological malignancies.
- Approximately 75% of the patients who could benefit from stem cell transplantation do not have a histocompatible related donor. For these patients, stem cell transplantation from an unrelated donor can be appropriate. However, for 20% of Caucasian and greater than 40% of non-Caucasian patients a suitable unrelated donor cannot be found.
- Expert opinion and some evidence support the centralization of such procedures in centres with a significant turnover. In the future, both accreditation and the supply of donor cells will require institutional centralization at the MUHC.
- *Advantages* of cord blood stem cells include 1) increased probability of transplantation since HLA-matching requirements are less strict, 2) more prompt availability (average 1-2 months difference), an obvious advantage when the time suitable for transplantation is strictly limited, 3). Less potential for transmission of viral infections such as CMV and EBV with cord blood.
- *Disadvantages* of cord blood stem cells include 1) generally longer time to hematopoieitic recovery, which may theoretically increase the hospital length of stay, 2) possible failure of the graft due to insufficient stem cells, an outcome that can usually be avoided by giving more than one unit.
- *On average***,** although there are differences in the clinical course, there is no consistent difference in the overall survival between cord blood and bone marrow transplants.
- *Mortality* in the early post-transplant years is high (50-65%), with 5-year mortality rates of approximately 75%. Although the number of patients with longer follow-up is small, survival after the fifth year is probably close to a near normal life expectancy. Based on our stated assumptions, we estimate that stem cell transplantation undertaken in a mix of cases similar to those currently treated at the MUHC, might result in an average 2.94 (95% CI: 2.58- 4.30) life-years gained per patient.

- *Cost* .We estimate that, excluding acquisition costs of the stem cells, the expected cost per adult patient to the MUHC for the transplantation and the first 10 years of follow-up after either bone marrow or cord blood transplantation would be approximately $57,255 (95% CI: $48,019-$60,735) and $60,591 (95% CI: 48,196 - $61,838) –respectively. We have assumed that the costs thereafter are negligible.

- *Acquisition cost of stem cells* is approximately $25,000 per unit. Bone marrow transplantations require one unit, and it has been assumed that cord blood transplantations in adults on average require two units. Thus, the average cost of a bone marrow transplantation in adult patients is approximately $82,000 and the average cost of a cord blood transplantation $110,500.

- *Cost-effectiveness*. The estimated cost effectiveness from the point of view of the healthcare system, of transplanting a mix of adult patients similar to those currently treated at the MUHC, would be $26,994 per life-year gained (95% CI: $22,000 - $43,000 – for bone marrow transplantation, and $36,633 per life-year gained(95% CI: $29,000 - $57,000) for cord blood transplantation. Both costs and life years were discounted at 3%.

- *Budget impact*. The number of additional adult patients who might receive stem cell transplantation at the MUHC if budget restraints were removed is uncertain. In 2003, there were 53 bone marrow or peripheral blood stem cell transplantations, and 4 cord blood transplantations, while 10 patients were transferred to another center. Furthermore, it is estimated that perhaps 10 patients may have died without transplantation due to the unavailability of facilities. As a first approximation, let us assume that there would be 20 additional stem cell transplants, 10 using bone marrow and 10 using cord blood. Discounting costs and health benefits at 3%, this would add approximately $1,850,000 to the MUHC budget in the first year, increasing to approximately $1,900,000 by the 10^{th} year, remaining constant thereafter. This intervention might result in an aggregate gain of 59 life-years (3% discounting).

- *Opportunity Costs*. If such an intervention were undertaken (increasing stem cell implants by 20 per year) in the absence of any corresponding budget increaseit seems certain that the commitment of $1,900,000 per year would have some negative effects on the health services offered by the institution (although the precise source of the necessary funds cannot be identified). It must be considered whether these would be greater or less than the anticipated health impact of such a policy.

Conclusions

- In spite of its high initial mortality and high costs, stem cell transplantation from either bone marrow/ peripheral blood or cord blood is a clinically effective therapy for appropriately selected patients, with an acceptable cost-effectiveness ratio.

<u>Recommendation 1.</u> The MUHC should urgently seek designated funding to enable it to offer this technology to appropriate adult patients and to support a transplant centre of sufficient quality to maintain good clinical outcomes and to assure the accreditation on which the future supply of donor cells will depend.

- The opportunity costs associated with even a modest increase in activity of 20 patients per year (approximately $1.8 million) would be too great a budgetary commitment in the absence of additional funding.

<u>Recommendation 2.</u> It is therefore recommended that no significant increase in stem cell transplantation be authorized in the absence of additional funding.

- Hematopoietic stem cell transplantation is an accepted therapy at the MUHC. In spite of the higher cost of cord blood transplantation it would be ethically difficult to refuse it to appropriate recipients for whom matching bone marrow stem cells can not be found.

<u>Recommendation 3</u>. The present practice of applying for special funding for each such case is fully justified and should be continued.

- The projected volume of stem cell transplantation activity would fully justify the existence of a stem cell centre at the MUHC. In the future it will not be possible to maintain transplant centers in each of the component hospitals of the MUHC.

<u>Recommendation 4</u>. All adult stem cell transplants carried out at the MUHC should take place in one designated centre.

Glossary

95% CI - 95% confidence interval

ALL – acute lymphoid leukemia

Allogeneic stem cell transplantation – transplantation performed with stem cells collected from another person (donor), related (family) or unrelated[1].

AML – acute myeloid leukemia

Autologous stem cell transplantation – transplantation performed with stem cells previously collected from the patient who is receiving the transplantation [1].

BMT – bone marrow transplantation

CBMTG – Canadian Bone and Marrow Transplant Group

CML – chronic myeloid leukemia

Conditioning regimen - treatment administered as a preparation for the stem cell transplantation, consisting of high dose-chemotherapy with or without radiotherapy in order to ablate the patients bone marrow and treat the underlying disease[2].

Engraftment – production of new blood cells in the recipient's bone marrow originating from the donor's hematopoietic stem cells [2]

Graft-versus Host disease (GVHD) – Reaction resulting from recognition by the donor's immune system of the recipient's tissues as foreign [1].

Graft-versus leukemia (GVL) effect – destruction of the malignant cells of the recipient recognised as foreign by the donor's immune system [1].

Hematopoietic stem cell – cells that differentiate into different types of blood cells[3]

Human-leukocyte antigens (HLA) – antigens that determine the immunological identity of the cell [1].

LYG – life-years gained

Myeloablative treatment – chemotherapy with or without radiotherapy used to destroy the hematopoietic system of the patient[1]. Used in preparation for the hematopoietic stem cell transplantation

NMDP – National Marrow Donor Program

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1. Introduction

Destruction of the bone marrow can occur as a result of certain diseases, or more frequently following the use of myeloablative chemotherapy or radiotherapy in the treatment of hematological malignancies[4]. When this occurs the bone marrow can be reconstituted by the infusion of stem cells that have the potential to multiply and to differentiate into the various cell types that constitute the normal bone marrow[4].

Stem cells for this purpose can sometimes be obtained from the patient's own bone marrow or peripheral blood (autologous transplantation) or from the bone marrow or peripheral blood of suitable HLA matched donors (allogeneic transplantation), who may be related or not to the patient [5]. When a related donor is not available it is necessary to find a suitably matched unrelated donor, a process which can be difficult[6 7] and time-consuming[7 8]. Because of this, increasing use is now being made of stem cells derived from the umbilical cord blood of newborn infants[9].

Cord blood cells have advantages and disadvantages. It is thought that cord blood T cells are more naïve than those derived from bone marrow or peripheral blood and consequently are less apt to be rejected or to cause graft-versus-host disease (see Appendix 1). As a result, cord blood stem cells may increase the chance of finding a suitably matched stem cells donor [9]. However, because of a lower cell dose per unit of cord blood engraftment is slower and sometimes unsuccessful[10]. Also, with cord blood, there is a lesser potential for transmission of viral infections such as CMV and EBV [11] and HHV-6, which can be detrimental to transplant outcome and increase the costs in terms of investigation and treatment (Dr. David Mitchell, Personal communication).

A disadvantage is that each placenta contains only a limited number of stem cells. Consequently in adults, particularly in larger adults, engrafting is less certain and takes longer, resulting in longer periods of vulnerable immunosuppression[7].

Transplantation of stem cells from bone marrow and peripheral blood is now an accepted therapy, with more than 16,500 procedures performed in Europe in 2001[12]. In 2003, 53 stem cell

transplantations from bone marrow or peripheral blood were performed at the MUHC, of which 87% were autologous or allogeneic from related donors[13]. In addition, 4 transplantations were performed with cord blood.

Strict HLA-matching is necessary with bone marrow and peripheral blood transplantation in order to avoid rejection of the infused donor's cells, which can be fatal[7]. Unfortunately, only approximately 20-25% of the patients are able to find a suitable matched bone marrow sibling donor[5], while the likelihood of not finding a suitable unrelated donor is approximately 20-25% in Caucasians, but greater than 40% in other ethnic groups[14].The likelihood of finding a matched unrelated donor has increased in recent years as bone marrow banks have grown[8].

Moreover, due to rapid disease progression, some patients do not survive long enough for a donor search[6], which takes approximately 2-3 months[6 7]. Even when a matched donor is found, approximately 30% of Canadian patients do not proceed to transplantation, half of the time due to death or progression of the disease[8]. Donor attrition is another obstacle [6]. With the increase in blood bank donors, the probability of finding a suitable donor may increase further[8]. Public bone marrow/peripheral blood banks worldwide currently have approximately 8.5 million donors listed, 226,000 in Canada, while cord blood banks have approximately 155,000 units worldwide[15].

The collection of stem cells from the bone marrow and peripheral blood is associated with some risks and in the case of bone marrow collection, the use of an operating room and general or epidural anesthesia, while cord blood is collected at the time of birth with no reported adverse effects to the child or mother[10]. Cord blood transplantations from related and unrelated donor were first carried out in 1988 and 1993 respectively[7].

For patients who cannot find a suitable donor, cord blood banks may increase the probability of transplantation due to the less strict HLA-matching requirements for cord blood transplantations[9]. Cord blood units are also available more promptly than bone marrow/peripheral blood units, which constitutes an advantage for patients who need an urgent stem cell transplantation[16]. There is also a lower possibility of transmission of viral infections,

such as cytomegalovirus (CMV), and Epstein-Barr virus (EBV)[11]. The principal advantages and disadvantages of the use of cord blood compared to bone marrow or peripheral blood stem cell transplantation are summarised in Appendix 1.

2. Stem Cell Transplantation Statistics

According to the Canadian Bone and Marrow Transplant Group (CBMTG), a total of 1,375 stem cell transplants were done in Canada in 2003 in adult and pediatric patients, including 361 in Quebec[13].

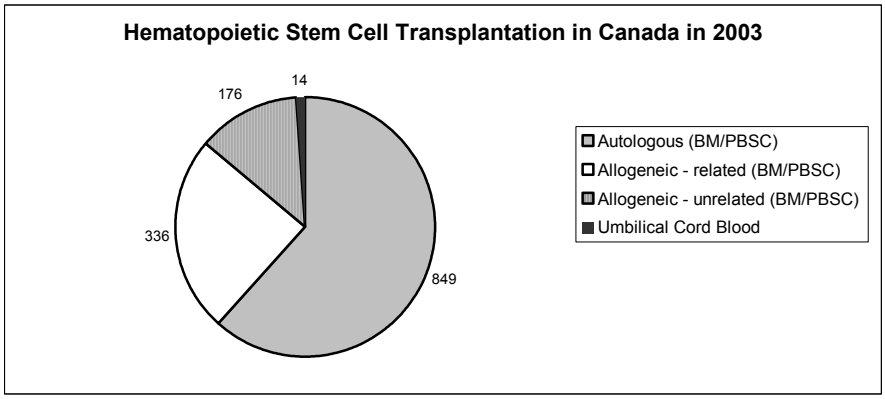


Figure 1 – Types of stem cell transplant performed in Canada in 2003[13]. Initially cord blood transplants were carried out in children, but the demand for adults now exceeds the demand in children and is likely to continue to increase in the future[17].

In 2003, about 2,000 cord blood transplantations were performed worldwide[7], but only 14 were done in Canada, of which 12 were done in Quebec[13].

There are six hospitals in the Province of Québec that perform stem cell transplants, four in Montreal and two in Québec City[13]. The Hospitals that perform stem cell transplantations in Montreal are: MUHC, Hôpital du Sacre-Coeur, Hôpital Maisonneuve-Rosemont, and the Hôpital Ste. Justine[13]. The hospitals that perform stem cell transplantations in Québec City are: Hôpital du Saint Sacrement, and Hotel-Dieu de Quebec[13].

The MUHC was the first Canadian centre to perform an adult cord blood transplantation (Dr. Pierre Laneuville, personal communication), and is currently the only Quebec hospital to perform both adult and pediatric transplants[13]. In 2003, the MUHC has performed 4 of the 14

cord blood transplantations performed in Canada (adult and pediatric), and the Hôpital Ste. Justine, has performed 8 of the 14 cord blood transplantations performed in Canada in 2003[13].

Both the Royal Victoria Hospital and the Montreal General Hospital perform autologous and allogeneic stem cell transplantations from related donors. However, the stem cell transplantation centre at the Montreal General Hospital is gradually shifting its patients to the Royal Victoria Hospital, and eventually the MUHC will have one centre performing adult stem cell transplantations, situated at the Royal Victoria Hospital (Dr. Pierre Laneuville, Personal communication).

Figures 2, 3, and 4 show the number of stem cell transplantations performed in Canada, Quebec, and MUHC in the past 3-8 years[13]

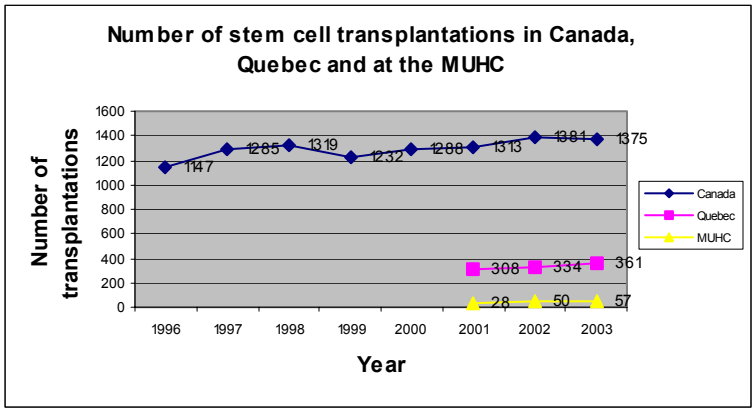


Figure 2 – Number of stem cell transplantations (bone marrow, peripheral blood, cord blood) in Canada, Quebec, and at the MUHC[13]

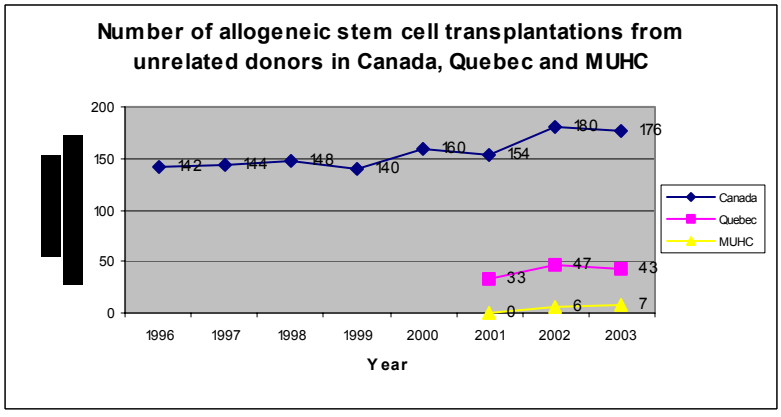


Figure 3 – Number of allogeneic stem cell transplantations from unrelated donors (bone marrow and peripheral blood stem cells) in Canada, Quebec, and at the MUHC [13]

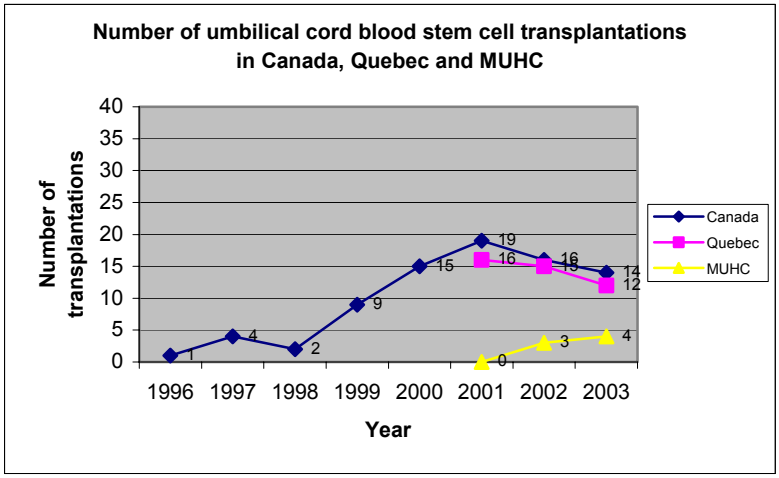


Figure 4 – Number of cord stem cell transplantations in Canada, Quebec, and at the MUHC[13]

3. Cord Blood Transplantation

3.1 Cord blood collection and preservation

Cord blood is collected from the umbilical cord and placenta of healthy newborns after the delivery of the placenta or during the third stage of labour, cryopreserved[7], after which it can then be stored for up to approximately 10 years[8]. Since HLA-typing and screening for infectious diseases are performed before freezing[8], cord blood can be made available to transplant centres within 2 weeks for cord blood[5] compared to 2-3 months with bone marrow or peripheral blood[16].

3.2 Search for a cord blood unit

When unrelated allogeneic stem cell transplantation is required, national and international blood banks are searched. If the patient requires an urgent transplantation, cord blood transplantation is indicated[6]. In non-urgent cases, the search for a bone marrow/peripheral blood unit can be continued, and, only if a such a unit cannot be found would cord blood be used [6]. According to Dr. Pierre Laneuville (Personal communication), this is the MUHC procedure.

3.3 Transplantation procedure and pre-treatment

For hematological malignancies, patients must first undergo a conditioning treatment consisting of chemotherapy and/or radiotherapy[7] to induce immunosuppression so as to avoid rejection of the stem cells and to eradicate residual malignant cells[18]. After the conditioning

treatment, the frozen stem cells sample is thawed at the bedside[19], and infused intravenously over a few minutes. The patients experience a critical period of immunosuppression caused by the bone marrow ablation, leaving them at risk for opportunistic infections[20]. The recovery of the patient's immune system depends on the engraftment and proliferation of the donor's stem cells infused[19].

At the MUHC the patients undergoing stem cell transplantations stay in a private room equipped with air filters for the remainder of the hospitalisation. Transfer to the ICU may be necessary for very ill patients. Prophylactic treatment for GVHD[21], and opportunistic infections[7] is normally used.

Factors that influence the outcome of the transplantation are the susceptibility of the malignancy to the chemotherapy or radiation, the occurrence of GVL and GVHD effects, and the patient's overall clinical status [7]. A higher number of nucleated cells available in the transplantation unit[6], and a higher degree of HLA-matching[7] have also been shown to be predictors of improved treatment outcomes.

3.4 Organization of stem cell transplantation.

Expert opinion and some direct evidence indicates that higher annual institutional volume is associated with better patient outcomes[6 17]. Furthermore, minimal annual volumes of transplantation are included in the criteria for the accreditation of transplantation centers[23]. American guidelines for standards on the handling of human cells, tissues, and organs for transplantations[22 23] have been developed by accreditation agencies in the United States and Europe[24 25]. In order to receive accreditation, the programs must have a dedicated transplant director who oversees a multi-disciplinary team, and laboratory and clinical services working under prescribed operating procedures. Additionally, patients' outcomes and complications must be kept in a database. Accreditation will be mandatory in the near future, and then only accredited programs will be able to receive stem cell units for transplantation. Moreover, as accreditation defines the standards of quality control, governmental agencies may also withdraw funding or close non-accredited programs (Dr. Pierre Laneuville, Personal communcation).

3.5 Indications for stem cell transplantation

Stem cell transplantation is indicated for some sub-types of different malignant diseases such as acute and chronic leukemias, non-Hodgkin's lymphoma, Hodgkin's disease, myelodysplastic syndrome among others[26], as well as non-malignant diseases such as hemoglobinopathies, marrow failure syndromes, inherited immune system, metabolic or platelet disorders among others[26].

The standard criteria for allogeneic or autologous transplantation from any source are[27]:

- Age < 55 years for allogeneic, and < 70 years for autologous;
- Absence of significant comorbidities with appropriate cardiac, pulmonary, hepatic, and renal function;
- Patients' ability to understand and agree to the treatment.

3.6 Cord Blood Banks

Cord blood banks were first created in New York, Milan and Düsseldorf in 1993, but others have since been created worldwide. According to the Bone and Marrow Donors Worldwide estimates, in 2003 there were approximately 155,000 cord blood units available [15].

Currently, there are two public cord blood banks in Canada, one in Alberta (http://www.acbb.ca/ACBBmain.htm), and one in Quebec (http://www.hema-quebec.qc.ca/E/anglais.htm).

4. Methods

4.1 Literature Review

A literature search was carried out to identify all clinical studies of cord blood transplantation from unrelated donors with more than 10 patients. Technology assessment reports and cost analyses were also identified. The literature review process is given in Appendix 2.

4.2 Economic Analysis of unrelated stem cell transplantation

Estimation of budget impact was carried out from the point of view of the MUHC. For this purpose costs that are not normally attributable to the MUHC budget, such as professional fees, and outpatient medication costs, were not included. In estimating the cost

effectiveness of these proceedures, however, we adopted the perspective of the Provincial Health Care System and included hospital, inpatient and outpatient medication costs, and physicians' and nursing fees. Additional overhead costs and costs with bone marrow or peripheral blood stem cells harvesting were not added to the hospitalisation costs. We included transplantation costs and those incurred in the following 10 years. Thereafter, the limited information available indicates that most patients can be considered virtually "cured", and we have accordingly ignored the costs beyond year 10.

Costs are given in 2004 Canadian dollars.

Treatment costs calculations:

Costs during the initial cord blood transplantation hospitalisation:

Hospitalisation costs were derived from the average cost of the patients transplanted in the MUHC in 2004. The costs included nursing and transplant coordinator costs, pharmacy, supplies, imaging and diagnostic tests, laboratory, HLA-matching, and stem cells laboratory (personnel, supplies, virology and microbiology tests) costs. The costing information was provided by Mr. Paul Tan (Finance Department).

We have compared the estimated hospitalisation costs at the MUHC with the costs obtained in other publications (Appendix 13).

Costs after hospital discharge

- Transplant to 100 days.We have assumed that the costs between hospital discharge and 100 days of follow-up post-transplant were the same as those reported in a study from Toronto[28]. Hospital readmission, intensive-care-unit (ICU), clinical, and day care visits, medications, laboratory and diagnostic tests, and hematologists' fees were included in the treatment costs.
- After 100 days: Costs were calculated by multiplying the rate of literature-reported complications by their estimated treatment costs. Physician's fees for the follow-up visits', and medication costs were also included. The rates of utilisation of these

resources were assumed to be similar between cord blood and bone marrow transplantation. Appendix 13 presents details about the treatment costs used.

Discounting

Costs and outcomes (life-years) incurred during the first year were not discounted, but those costs that occurred later were discounted at 3% and 5%. We have assumed that costs and outcomes in subsequent years occurred at the beginning of each year.

Cost-effectivenes analyses

We have carried-out incremental cost-effectiveness (ICE) analyses of cord blood and bone marrow/peripheral blood transplantations compared to no transplantation. The number of life-years gained was used as the comparative measure of effectiveness. ICE analyses were calculated using TreeAge software (TreeAge Pro 2004 Suite, TreeAge Software Inc.)

The costs were calculated as previously described. The survival in the cord blood group was based on our literature review. We have assumed that the survival after bone marrow/peripheral blood transplantations would be similar to cord blood transplantations, as there was no clear evidence of differences in survival between the groups in the literature. An expert estimate of the survival without transplantation in the same patient population was used in the no transplantation group.

Sensitivity Analyses

Probabilistic sensitivity analyses were performed by varying treatment costs and the probability of survival at different points both individually and simultaneously, i.e., one-way and multiway sensitivity analysis respectively. The sensitivity analyses were performed using Monte Carlo simulation with the TreeAge software (TreeAge Pro 2004 Suite, TreeAge Software Inc.). Appendix 15 presents the details of the sensitivity analyses performed.

5. Clinical results in adult patients

Appendices 5 and 6 present a summary of the design and characteristics of the studies included in this report.

Results of studies of cord blood transplantation in adult patients who received less aggressive conditioning treatment (non-myeloablative) and in pediatric patients are summarised in Appendices 7 and 8 respectively.

5.1 Description of the endpoints used

The definition of the endpoints may have varied from study to study, nonetheless, a general description is given in Appendix 3 in order to facilitate the interpretation of the findings.

5.2 Results in adult patients

Patient population

The majority of the patients included in the cord blood studies selected had acute or chronic leukemia and a median age from 26 to 43 years[29-31 32 33 34 35 36 37 38]. The majority of the transplants were done with 1 or 2 HLA-mismatches between the donor and the host and a median dose of nucleated cells infused between 15 million/kg to 25 million/kg [29-31 32 33 35 37 38]. Most adult patients had not found a suitably HLA-matched bone marrow or peripheral blood donor previously[29-31 32 33,34].

Survival

Early causes of death were regimen-related toxicity and infection, while, later, deaths included malignancy relapse, secondary cancer and GVHD[34]. The low rate of potentially fatal relapses occasionally may be due to the short follow-up (mean 20 months)[35].

As noted in section 5.7 below, there is great variability in the patient populations and in the details of treatment in reported series. The weighted average survival of all the series reflected in Appendix 6 is as follows.

- At 100 days: 49.5% [33 34]
- At 1 year: 32.5% [17 30 31 33 35 37]
- At 2 years: 31% [34 37]
- At 3 years: 24% [33,38]
- At 5 years: 23% [17]

Neutrophil recovery

The rate of neutrophil recovery at 42–60 days after the transplant varied from 65% to 90% [30,33 34 35 36 37,38]. One study reported a 100% rate of neutrophil engraftment in the adult patients who survived the 60 days post-transplantation[32].

Acute and Chronic GVHD

The severity of graft-versus-host disease (GVHD) is divided into four grades (see Appendix 4). The rate of acute GVHD grades II and higher varied between 26% and 73% in the adult studies selected [29 30-33 34 35 36 37,38]. One of the studies reported a 32 days median time (range 13-86 days) to develop GVHD grades II and higher[33]. GVHD is frequently fatal[32 33 35]. The rate of chronic GVHD varied between 30% and 50% of the adult patients who survived longer than 100 days in the largest studies [30-33 34 37,38].

Leukemia relapse

A 15%-23% rate of leukemia or lymphoma relapse was observed within 2 years of the transplant[29,31 36 37,38].

5.5 Post-Transplantation Complications

Complications that arise after stem cell transplantations, such as infections and GVHD[7 39] cause considerable morbidity and mortality (due to either the conditioning regimen or due to the transplantation)[19 40]. Severe prolonged hematopoietic suppression, and numerous other complications may occur early[19 40] Long-term complications are a consequence of either chronic GVHD, or of toxicity caused by the conditioning regimen[19].

Studies have reported GVHD rates and fatal complications, but no information on non-fatal complications was given [29-31 32 33 34 35 36]. There are some publications reporting complications following bone marrow, peripheral blood or cord blood transplantations (Appendix 10), however it is difficult to assess their generalisability to other stem cell sources (bone marrow, peripheral blood, cord blood), and other patient populations, also considering that different centres may use different conditioning regimens.

5.6 Comparisons between Cord Blood and Bone Marrow/Peripheral Blood Stem cell Transplantations

We identified ten non-randomised studies comparing cord blood and bone marrow/peripheral blood transplantations[1 36 37 38 41 42 43 44 45 38,46]. Limitations intrinsic to these studies do not permit firm conclusions to be drawn on the comparison of these two alternatives for stem cell transplantation. Nevertheless, results[1 36 37 38 38,41 42 43 44 45 46] are consistent with the hypothesis that cord blood transplantation may result in a longer time to neutrophil engraftment, but may present with a lower rate of acute GVHD compared to bone marrow/peripheral blood transplantations[21].

Laughlin et al. who compared the outcome of 150 patients who received cord blood with 450 who received bone marrow, observed no differences in treatment failure, overall mortality, transplant-related mortality, and disease relapse between patients who underwent cord blood transplantation with 1-2 HLA-mismatches compared to patients who underwent bone marrow transplantation with 1 HLA-mismatch[38], which may also have been due to insufficient statistical power to detect differences. However, in the same study, patients undergoing cord blood transplantation with 1-2 HLA-mismatches had a 1.5 fold increase (relative risk (RR) 1.5, 95% confidence interval (CI): 1.2,1.9) in overall mortality and a 1.9 fold increase (RR 1.9, 95% CI:1.5 , 2.5) in transplant-related mortality compared to patients undergoing matched bone marrow transplantation[38]. Rocha et al. compared the outcomes of 98 unmatched cord blood implants with 584 matched bone marrow transplants[37]. While the risk of acute GVHD was lower in the former, time to neutrophil recovery was significantly longer[37]. Overall, there was no statistically significant difference in the incidence of chronic GVHD, relapse rate, or transplant-related mortality[37].

In contrast, a single-centre study involving 113 Japanese patients showed improved rates of transplant-related mortality and disease-free survival with cord blood compared to bone marrow transplantations[36]. The authors consider that the improved mortality outcomes with cord blood compared to bone marrow transplantations may have been due to a lesser need for steroid treatment for GVHD, and genetic characteristics of the Japanese population[36].

More details about these comparative studies are given in Appendix 9.

5.7 Limitations of the published studies used in this report

The small number of patients included in some studies, and the fact that some of these studies included reports from several hospitals in different countries without clear evidence of standardisation of the measurement of the outcomes, may have resulted in a loss of accuracy in the overall study results[34 35 37 38,47]. Additionally, discrepancies between the results of the different studies may have also been caused by differences in the baseline characteristics of the patients included[29-31 32 33 34 35 36 37,38]. There may have been an overlap in the patients included in the different studies, since different reports included results from at the same hospital[29 30-32 36]. The fact that most studies included patients over a period of several years, may also add to the inaccuracy of the results[29-31 32 33 34 35 36], as the clinical practice and physicians' experience may have changed over the period. Moreover, most studies included patients with different malignant and non-malignant disorders [17 30 32 33 34 35 36] which makes extrapolation of their results to specific diseases difficult. The conditioning and prophylactic regimens also varied within and between the studies[29-31 32 33 34 35 36].

6. Technology Assessment Reports and Economic Studies

The general conclusions of previous Technology Assessment reports on cord blood transplantations are summarised here. Details are presented in Appendix 11.

Efficacy - In general, reports published before 2001 regard cord blood transplantations as a promising alternative but still in development, with only limited evidence of effectiveness in the literature [21 48 49]. The report from Alberta Heritage Foundation for Medical Research published in 2000 also concluded that the field was still evolving and there was not enough evidence to compare the effectiveness of cord blood transplantations with bone marrow or peripheral blood stem cell, [8]. Reports published after 2002 have concluded that cord blood transplantation is an acceptable treatment in patients without a bone marrow or peripheral blood donor with a suitable HLA-matching profile[50 51 52 53], although some authors have expressed more caution in adults due to the lower number of hematopoietic cells present in the cord blood unit[54]. Some authors also have doubted the validity of comparing alternatives due to the scarcity of published

comparisons[8 52 53]. According to the Biological Response Modifiers Advisory Committee (BRMAC) of the Food and Drug Administration (FDA), cord blood transplantations should be done with a maximum of 2 HLA-mismatches[52].

Costs – Reported hospitalisation costs for bone marrow or peripheral blood stem cell transplantations varied between CDN$34,643 and CDN$140,000 from sources such as observational studies[28], technology assessment reports[8] and governmental estimates from the provinces of Alberta [55]. One study found costs between CDN$8,729 and CDN$11,691 for the post-hospitalisation costs within the first 100 days after the transplantation[8 28 55].

Further details about these cost analyses are shown in Appendices 11-14.

7. Future Directions

Research is ongoing to improve the number of nucleated cells available in the cord blood unit (*ex vivo* expansion of CD34 cells, and co-transplantation of haplo-identical CD34+ cells), but these techniques are still investigational[7 56]. Improvements in the collection of the cord blood may also increase the number of cells available in the transplantation unit [7]. Increasing the transplanted cell dose will decrease immunocompromised time[57] thereby improving the outcomes.

8. Local Experience

The information on local practice was provided by Dr. Pierre Laneuville (Personal communication).

At the MUHC, stem cell transplantations in adults are performed according to the established clinical standards listed earlier. These are mainly hematologic malignancies, not expected to be cured with chemotherapy or radiotherapy. Cord blood transplantations are carried out in patients for whom no suitable bone marrow or peripheral blood donors could be found.

In 2003, the MUHC performed 53 bone marrow or peripheral blood transplantations, mostly autologous or allogeneic with related donors, and 4 allogeneic cord blood transplantations from unrelated donors. The Division of Hematology aims to reach a level of approximately 100

transplants per year within the next five years. The MUHC is the only centre in Montreal having performed cord blood transplantations in adults[13]. Both the Royal Victoria Hospital and the Montreal General Hospital perform autologous or allogeneic stem cell transplantations from related donors. However, the stem cell transplantation centre at the Montreal General Hospital is gradually shifting its patients to the Royal Victoria Hospital, and eventually the MUHC will have one centre performing adult stem cell transplantations at the Royal Victoria Hospital.

Presently, the number of both cord blood and bone marrow or peripheral blood stem cell transplantations at the MUHC is limited by infrastructure and budget. In the case of allogeneic unrelated bone marrow or cord blood, funding is not available to cover the additional cost of search and procurement of the stem cells approximately CDN$25,000 per unit[8]. As a consequence of this lack of funding, approximately 10 patients requiring allogeneic stem cell transplantations from unrelated donors per year have to be referred to another hospital in Montreal. In other provinces, and in certain Québec hospitals, the costs of stem cell transplantation are covered by a designated budget and are not included in the hospitals' global budget allocation.

9. Health Benefits, Budget impact and cost-effectiveness.

In 2003, the MUHC budget absorbed the costs of 57 stem cell transplantations, 4 from cord blood, and 53 from bone marrow or peripheral blood, mostly autologous or from related donors. An additional 10 patients were referred to another hospital and an unknown number of potentially appropriate patients received no transplantation, for fiscal reasons. The exact increase in transplants that might result from relief of the budgetary constraints is unknown. For the purposes of the following estimates we will assume that 20 additional allogeneic unrelated donor transplants would be carried out each year, 10 bone marrow and 10 cord blood.

Health benefits.

Based on information from the literature, we have estimated that 78 life-years may be gained as a result of transplantation of an additional 20 adult patients who receive allogeneic stem cell transplantation from unrelated donors at the MUHC, or 59 discounted at a 3% (See Appendix 14 for details).

The quality of life of those who survived the procedure would initially be poor. However, according to a study by Baker et al., 70% of the patients with chronic myeloid leukemia who survived for at least 2 years after an allogeneic bone marrow transplantation from an unrelated donor considered their overall health as good to excellent, although patients who developed chronic GVHD, approximately 38% of their sample, are 2.4 times more likely to rate their overall health as poor[58]. Messner et al. found that, while within the first 3 years after an allogeneic stem cell transplant (75% from related donors), patients who were long-term survivors showed decreases in stamina, ability to concentrate, and physical ability, after 3 years, the patients' quality of life was closer to the normal population [59] (see appendix 12).

Budget impact

Details about the economic analysis are given in Appendix 13.

According to Dr. Pierre Laneuville, adult patients need 1 stem cell unit with bone marrow/peripheral blood and 2 units with cord blood[A], at a unit cost of $25,000.

- We have estimated that the cost for an allogeneic transplantations in an adult patient using an unrelated donor at the MUHC would be approximately **$82,000** for bone marrow, and **$110,500** for cord blood transplantation, including the initial hospitalisation cost, other hospitalisation and treatment costs up to 10 years after the initial hospital discharge, and the cost of procurement of a stem cell unit (3% discounting). This estimate relies on assumptions that are explained in Appendix 13.

Acceptance of an additional 20 allogeneic stem cell transplantations from unrelated donors per year, half from bone marrow/peripheral blood, and half from cord blood, the additional cost would be approximately $1,900,000 to the MUHC budget (see Appendix 13).
For comparison, the cost for each transplantation from a related donor would be $25,000 to $50,000 lower, due to a saving of $25,000 per case for acquisition costs.

[A] Due to the lack of comparative data in the literature, we have assumed that the short and long-term response to a transplantation using 2 cord blood units would be the same as that using 1 cord blood unit, however, using more than 1 unit might theoretically result in a faster engraftment and consequently a shorter hospital stay.

Cost-effectiveness

Only very approximate cost-effectiveness ratios can be provided. We have estimated that, from the point of view of the Provincial healthcare system, and discounting both costs and life-years at 3%, the cost per life-year gained of performing stem cell transplantation in adult patients from an unrelated donor at the MUHC is $26,994 (95% range $22,000-$43,000) for bone marrow and $36,633 (95% range: $29,000-$57,000) for cord blood (see Appendices 14 and 15).

10. Discussion

This review was carried out to find answers to two questions: 1) Should the MUHC expand the use of stem cell transplantation through use of cord blood ?, and 2) Are the health benefits of stem cell transplantation, regardless of the source of cells, sufficiently great to justify increasing its availability in the absence of any corresponding increase in budget?

1) Use of cord blood. As regards the first question it is relevant to recall that stem cell transplantation from bone marrow is already an accepted intervention at the MUHC, and the available evidence suggests that the outcome of cord blood transplantation is broadly equivalent to that of bone marrow. By use of cord blood the benefits of stem cell transplantation can be made available to those patients for whom matched donor cells from bone marrow or blood cannot be found, or cannot be obtained sufficiently rapidly. Thus the only reason not to use cord blood for such patients would be the increased cost ($25,000 per transplantation, due to the need for, on average, two units of cord blood). A decision to not provided cord blood to patients who would presumably otherwise not survive would be ethically difficult to countenance.

2) Extension of stem cell transplantation at the MUHC. Should the health benefits of this technology be made available to an increased number of adult patients in the absence of any corresponding increase in the budget? In considering this issue it must again be remembered that stem cell transplantation is already an accepted technology at the MUHC, and that for the fortunate patients for whom a family donor can be found, the issue of cost is not at issue. It is only the additional $25,000,(the cost of obtaining a matched, unrelated unit),or $50,000 (for two cord blood units), that distinguishes these proceedures transplantations from related donors.

Although uncertain, it is considered likely on grounds of demand that an additional 20 adult patients (10 bone marrow/blood and 10 cord blood) might be transplanted each year in the absence of budget restraints. Of these, 10-12 would probably not survive the first year, and thus would not experience any significant extension of life. However, between 5-7 patients would achieve many years of life of very acceptable quality. We estimate that overall, there might be gain of 59 life-years, at cost of $1,900,000 (3% discounting).

Finally, in making these decisions the overall cost effectiveness of stem cell transplantation is relevant. The estimated cost per life-year gained is approximately $27,000 for bone marrow, and $36,500 for cord blood (3% discount rate). These values are slightly higher than those commonly recommended by the TAU for acceptance. However, other technologies with higher cost-effectiveness have previously been accepted at the MUHC, such as implantable cardiac defibrillators, $47,458 [60], or renal hemodialysis, approximately $85,000[61].

These results should be interpreted with caution. There is not enough information in the literature to permit firm estimates of survival benefits or costs, nor is there sufficient information on which to base cost comparisons between patients receiving allogeneic transplantations from related and unrelated donors, and the results rely on assumptions described in Appendix 13. Nevertheless, these considerations have led the committee to the following conclusions.

Conclusions

- In spite of its high initial mortality and high costs, stem cell transplantation from either bone marrow/ peripheral blood or cord blood is a clinically effective therapy for appropriately selected patients, with an acceptable cost-effectiveness ratio.

<u>Recommendation 1.</u> The MUHC should urgently seek designated funding to enable it to offer this technology to appropriate adult patients and to support a transplant centre of sufficient quality to maintain good clinical outcomes and to assure the accreditation on which the future supply of donor cells will depend.

- The opportunity costs associated with even a modest increase in activity of 20 patients per year (approximately $1.8 million) would be too great a budgetary commitment in the absence of additional funding.

<u>Recommendation 2.</u> It is therefore recommended that no significant increase in stem cell transplantation be authorized in the absence of additional funding.

- Hematopoietic stem cell transplantation is an accepted therapy at the MUHC. In spite of the higher cost of cord blood transplantation it would be ethically difficult to refuse it to appropriate recipients for whom matching bone marrow stem cells can not be found.

<u>Recommendation 3</u>. The present practice of applying for special funding for each such case is fully justified and should be continued.

- The projected volume of stem cell transplantation activity would fully justify the existence of a stem cell centre at the MUHC. In the future it will not be possible to maintain transplant centers in each of the component hospitals of the MUHC.

<u>Recommendation 4</u>. All adult stem cell transplants carried out at the MUHC should take place in one designated centre.

Appendix 1 - Advantages and Disadvantages of the Use of Cord Blood Compared to Bone Marrow or Peripheral Blood Stem Cells

Advantages of cord blood transplantation (UCBT) compared to bone marrow/peripheral blood stem cells transplantations (BMT/PBSCT)

- Less strict HLA-match requirement in UCBT compared to BMT/PBSCT [10]. This may increase the likelihood of patients with uncommon HLA types to find a UCB donor, compared with BMT/PBSCT[9];
- Lower immune reactivity due to the immaturity of the immune system of the neonate compared to adults, which may, as a consequence, result in a lower incidence of graft-versus-host disease (GVHD)[62], a potentially fatal complication[7]
- Absence of risk to donors[10];
- Lower risk of transmission of infections such as cytomegalovirus (CMV), and Epstein-Barr virus (EBV)[11] due to the lower prevalence of infections in neonates[63];
- Ability to expand in vitro[62];
- Decrease in the waiting time to obtain a sufficiently HLA-matched donor compared to BMT/PBSCT, as the UCB unit had already been collected and cryopreserved[62], which is especially advantageous in urgent cases[6];
- the presence of more primitive stem cells, which can produce long-term repopulating cells in vivo[62];
- the production of larger colonies when stimulated by growth factors[62].

Disadvantages of UCBT compared to BMT/PBSCT

- A smaller number of cells in the sample, which may predispose the patients to a higher risk of infections due to a longer time for the hematopoietic recovery, especially in adults[7]. Techniques are being studied in order to overcome this limitation[7];
- The greater immaturity of the neonate's immune system may also result in a lower graft-versus-leukemia (GVL) effect[62], which happens when the donor's immune system recognizes as foreign and destroys the host's malignant cells[7]. Theoretically, a lower GVL effect may result in a higher risk of recurrence of the leukemia[10]. Although this has not been found in practice [37] [38].

Appendix 2 – Literature Review Process

The literature search was performed by using the Pubmed and EMBASE databases, and the Cochrane Database of Systematic Reviews. The search terms included: 'stem cells', and 'cord or umbilical', and 'transplantation'. There were no restrictions for dates of publication or languages, however, only articles published in English, French, German, Italian, Spanish, and Portuguese were reviewed for relevance. The clinical and economic studies selected had to meet the following criteria:

- Studies in humans;
- Studies of cord blood transplantations from unrelated donors;
- Studies conducted specifically in patients with hematological malignancies, or whose study population included at least 50% of patients with hematological malignancies;

Studies were excluded from our review if they had any of these characteristics:

- Case reports of 10 patients or less, as these studies are more prone to biases;
- Studies conducted specifically in patients with diseases other than hematological malignancies.

Studies that included adult and pediatric patients as one group and from which separate results for each of these two categories could not be derived were not included in our report, such as the reports from the New York Blood Center[9], Eurocord [64], and from the Japanese Cord Blood Bank Network[65].

The reference lists of the clinical and review studies selected were also searched in an attempt to find additional clinical studies that might have been missed during the literature search. For the same reason, specific journals of the field (*Bone Marrow Transplantation, Blood, Biology of Bone Marrow Transplantation*) were also manually searched with the keywords "cord", "umbilical", and "stem cell", used individually. References that consisted of abstracts from conferences for which the full publication was not available were verified, however, their results were only included in the report if they contained additional information that could not be found elsewhere.

Twenty clinical studies that met our eligibility criteria were identified in the literature, 11 in adult patients [17 29-31 32 33 34 35 36 37 38] in 9 in pediatric patients[1 42 66,67 47,68 69 70 71]. Four studies of cord blood transplantations following non-myeloablative regimens were found in the literature[72 73 74 75]. The studies consisted mostly of non-comparative observational studies of cord blood transplantations in patients who could not find a bone marrow/peripheral blood donor[29-31 32 33].

We have identified 10 studies that consisted of non-randomised comparisons between cord blood and bone marrow/peripheral blood transplantations [1 37 38 41 42 45 36 43 44 46].

Technology Assessment Reports and Economic Analyses

Health technology agencies databases were also searched with the keywords "cord", "umbilical", and "stem cell", used individually. A total of ten reports from health technology agencies were identified, however, a report performed by the Australian Health Technology Advisory Committee[76] was not available, and three reports, published by the Norwegian Centre for Health Technology Assessment[54], the Swedish Council on Technology Assessment in Health Care[48], and by the Health Council of the Netherlands[77] could not be translated, but information from the executive summary of these reports is presented in this report. The results of the remaining 6 reports are summarised in this report [8,21 50 53 49 78]. Four economic analysis on stem cells transplantations identified are included in this report[28 79 80 81]

A list of the health technology assessment databases used in the literature search is given below.

Economic Analyses

One economic analysis on allogeneic stem cell transplantation was found in the literature[82].

List of health technology assessment databases used in the literature search

Health Technology Assessment Agencies:

- CHSPR – Centre for Health Services and Policy Research (UBC) British Columbia
- HSURC – Health Services Utilization and Research Commission (Saskatchewan)
- ICES – Institute for Clinical Evaluative Sciences
- MCHP – Manitoba Centre for Health Policy
- INAHTA database – International Network of Agencies for Health Technology Assessment

Members of INAHTA (agencies included in the INAHTA database):

AÉTMIS - Agence d'évaluation des technologies et des modes d'intervention en santé

AHFMR - Alberta Heritage Foundation for Medical Research

ANAES - L'agence nationale d'accréditation et d'évaluation en santé

ASERNIP-S– Australian Safety & Efficacy Register of New Interventional Procedures - Surgery

CAHTA - Catalan Agency for Health Technology Assessment and Research

CCOHTA – Canadian Coordinating Office for Health Technology Assessment

CÉDIT – Comité d'évaluation et de diffusion des innovation technologiques

CMT – Center for Medical Technology Assessment (Sweden)

DACEHTA – Danish Centre for Evaluation and Health Technology Assessment

DIMDI – German Institute of Medical Documentation and Information

DSI – Danish Institute for Health Services Research

FinOHTA – Finnish Office for Health Care Technology Assessment

ITA – Institute of Technology Assessment ((Austria)

MSAC – Medical Services Advisory Committee (Australia)

NCCHTA - National Coordinating Centre for Health Technology Assessment

NHS QIS - NHS Quality Improvement Scotland

NHS – National Horizon Scanning Centre

NICE – National Institute for Clinical Excellence

SBU – The Swedish Council on Technology Assessment in Health Care

SNHTA – Swiss Network for Health Technology Assessment

TA-SWISS – Center for Technology Assessment

Appendix 3 - Description of the endpoints used

The definition of the endpoints used may have varied from study to study, however, a general description is given below in order to facilitate the interpretation of the findings:

Disease-free survival: period during which the patient has not experienced a leukemia relapse or death [32]

Event-free survival: period during which the patient was alive and did not received a second graft, or a bone marrow allotransplant or autograft, had no signs of autologous reconstitution or disease relapse[33].

GVHD: evaluated according to standard criteria[34 63]. See appendix 4 for more details.

Relapse: presence of morphological evidence of disease[36 69].

Secondary graft failure: loss of an engrafted transplant[32 33].

Survival: overall survival throughout the study period, calculated by the Kaplan-Meyer curve [63 11].

Time to neutrophil recovery: time until recovery, i.e., the first of three consecutive days after transplantation during which the absolute neutrophil count (ANC) was above 500 per cubic millimeter[36 1 69].

Time to platelet recovery: the first of seven days during which the platelet count was above 20,000 per cubic millimeter[36 69].

Transplantation-related mortality: death due to complications related to the transplant such as GVHD or infection and not due to the malignancy[7].

Appendix 4 – GVHD Grading

The table below contains the recommended staging and grading of acute GVHD in the different organs [83].

Table 1– Acute GVHD stages and grades

	Organs involved		
Stage	Skin	Liver	Gut
1	Rash on < 25% of the skin	Bilirubin 2-3 mg/dl	Diarrhea > 500 ml/day or persistent nausea
2	Rash on 25-50% of the skin	Bilirubin 3-6 mg/dl	Diarrhea > 1000 ml/day
3	Rash on > 50% of the skin	Bilirubin 6-15 mg /dl	Diarrhea > 1500 ml/day
4	Generalised erythroderma with bullous formation	Bilirubin > 15 mg/dl	Severe abdominal pain with or without ileus
Grade			
I	Stage 1-2	None	None
II	Stage 3 or	Stage 1 or	Stage 1
III	-	Stage 2-3 or	Stage 2-4
IV	Stage 4 or	Stage 4	-

Source: Przepiorka et al. [83].

Appendix 5 – Characteristics of the studies included in the report

Adult patients

The outcomes of 57 adult patients with malignant or non-malignant diseases who received a cord blood transplantation from unrelated donors at the Duke University Medical Center between January 1996 and January 2002 were published by Long et al.[33]. According to the authors, 19 patients included in this report had already been included in a publication by Laughlin et al.[34], although with a shorter follow-up[33]. The UCB units were obtained mostly from the New York Placental Blood Program (NYPBP), but some units were obtained from the Cord Blood Transplantation Study bank, and from the National Marrow Donor Program[33]. Patients who did not have a related donor with none or one HLA-mismatch or whose disease did not allow enough time to obtain a sample from matched unrelated donor were included in this study[33]. The patients received the conditioning regimen according to their underlying disease[33].Granulocyte colony stimulating factor (G-CSF) was administered to the patients until neutrophil recovery was obtained[33]. Heparin was administered from the start of the conditioning regimen until neutrophil recovery in order to avoid veno-occlusive hepatic disease[33]. The patients also received GVHD and infections prophylaxis[33]. The median follow-up was 4.6 years[33]. The study has included a relatively large number of patients from one institution and the follow-up was long, however, changes in clinical practice may have occurred within the 6 years during which the patients were included. There was an overlap between the patients in this publication[33] and those from a publication by Laughlin et al.[34] as mentioned earlier.

The outcomes of 68 adult patients with malignant and non-malignant diseases who received a cord blood transplantation from unrelated donors between February 1995 and September 1999 in different hospitals were reported by Laughlin et al. [34]. Patients who did not have an identically HLA-matched related or unrelated donor, or for whom a suitably HLA-matched bone marrow donor could not be found within 6-8 weeks were eligible for this study[34]. Most UCB units were obtained from the NYPBP, but some units were obtained from other UCB banks[34]. The conditioning regimen was chosen according to the underlying disease[34]. The patients received GVHD prophylaxis[34]. The median follow-up was 22 months[34].

The results of 22 consecutive adult patients with hematologic malignancies who received UCBT from unrelated donors between May 1997 and December 2000 at one hospital in Spain were reported by Sanz et al.[32]. Patients for whom HSCT was considered the best therapy, and who did not have a related donor with none or one HLA-mismatch, or for whom no identically HLA-matched BM donor could be identified were eligible[32]. The units were obtained from the Spanish Registry of Bone Marrow Donors[32]. The patients received GVHD prophylaxis, and G-CSF was administered from day 7 post-transplantation until neutrophil recovery[32]. The median follow-up was 8 months[32].

The results of 108 adult patients with malignant and non-malignant diseases who received a cord blood transplantation from an unrelated donor before January 2001 were published[35]. The publication includes the results from several European and non-European hospitals that reported the patients' outcomes to the Eurocord registry[35]. The UCB units were obtained from the Eurocord[35]. The median follow-up was 20 months[35]. The study included a large number of adult patients, however, these patients were included in a large number of sites from different countries, which did not necessarily follow the same treatment and transplantation procedures. This fact, together with the fact that the patient evaluation was done by a large number of investigators may have affected the accuracy of the overall results.

The results of 18 adult patients with AML who received cord blood transplantation from unrelated donors at the University of Tokyo Medical Science Institute between January 1999 and November 2002 were reported by Ooi et al.[29]. The patients received GVHD prophylaxis, and G-CSF was administered concomitantly with the conditioning regimen[29]. The patients were followed for 2 years after the transplantation[29]. The same author reported the results of patients with ALL[31], and patients older than 45 years[30] who underwent UCBT.

The outcomes of 113 patients undergoing BMT (n=45) and UCBT (n=68) in one institution in Japan between 1996 and 2003 were published by Takahashi et al.[36]. The baseline characteristics of the patients were different, for

this reason, multivariate analyses adjusting for variables that could influence the outcomes were done, however, it is not clear which variables were kept in the final model for each outcome[36].

Stevens et al. published the results of 391 adult patients who underwent UCBT in different countries with cord blood units from the New York Blood Center[17]. The results are published as an abstract from a symposium[17].

Laughlin et al. reported the results from 600 adult patients who underwent allogeneic stem cell transplantation from unrelated donors, 367 from matched bone marrow, 83 from 1-HLA mismatched bone marrow, and 150 from 1-2 HLA-mismatched cord blood[38]. The results reported were obtained from data reported from centres located throughout the world to the New York Blood Center and from the International Bone Marrow Transplant Registry (IBMTR) [38]. The transplantations occurred between January 1st 1996 and December 31st 2001 [38].

Rocha et al. reported the results from 682 adult patients who underwent allogeneic stem cell transplantation from unrelated donors between January 1st 1998 and December 31st 2002, 584 from bone marrow and 98 from cord blood[37]. The data were reported by centres located throughout the world to the Eurocord and to the European Blood and Marrow Transplant Group (EBMTR) [37].

Appendix 6 - Studies of Cord Blood Transplantations in adult patients (unrelated donors)

Study Characteristics

Observational studies / Year / Number of patients	Follow-up	Age (years) / Weight (kg) Median (range)	Underlying disease	HLA mismatch	Cell infusion (median)	Use of G-CSF / GM-CSF after transplantation	Period of inclusion of patients
Sanz et al. [32] (2001) N=22 Source of units: several banks	8 months (median)	Age: 29 (18 – 46) Weight: 69.5 (41-85)	CML: 12 (45%) ALL: 6 (27%) AML: 3 (14%) 15 (71%) – high risk Non-malignant disease: 1(5%)	None: 1 (5) 1: 13 (59%) 2: 8 (36%) >=3:0 (by design)	CD34+ cells/kg (median): 0.79 x 10^5 CFU-GM/kg: 1.77 x 10^4	Time from diagnosis, m (median): 10 m (5-125) Time from search, m (median): 4 (0.25 – 12)	1997 – 2000
Laughlin[34] (2001) N=68 Source of units: NY Blood Center	22 months (median)	Age: 31.4 (18-58) Weight: 69.2 (41- 116)	Acute / chronic leukemia: 51 (75%) 93% of which in intermediate or advanced stage Non-malignant disease: 14 (21%)	None: 2(3%) 1: 18 (26%) 2: 37 (54%)	Nucleated cells / kg: 21 million / 16 million after thawing	-	1995 – 1999
Gluckman[35] (2001) N=108 Source of units: Netcord	20 months (median)	Age (mean): 26 (15-53) Weight (mean): 60 (35 – 110)	Acute / chronic leukemia: 92/108 (85%) Non-malignant disease: 12(11%)	None: 6 (5.6%) >= 1: 102 (94.4%)	Nucleated cells/kg: 17 million		1988 – 2001 (adults and children)
Ooi [29](2004) N=18 (AML) Source of units: not specified	2 years	Age; 43 (range 21 – 52) Weight: 55.2 (36 – 62)	All acute myeloid leukemia 14 (78%): beyond 1st remission	None: 0 1: 4 (22%) 2: 9 (50%) 3: 4 (22%)	Nucleated cells/kg: 25.1 million/kg	All patients	1999 – 2002
Long[33] (2003) N=57 Source of units: several banks		Age: 31 (18-58) Weight: 70 (46-110)	Leukemia:44 (77%) Non-malignant disease: 7 (12%)	None: 2 (4%) 1: 8 (14%) 2:44 (77%) 3:3 (5%)	Nucleated cells/kg: 15 (5.4-27)	-	1996 - 2002
Takahashi[36] (2004) N=68 Japan cord blood bank	25 months (median)	Age: 36 (16-53) Weight: 55(36 – 76)	AML: 39 (57%) ALL 15 (22%) CML: 5 (7%) Advanced disease:41 (60%)	None: 0 1: 14 (21%) 2: 34 (54%) 3: 15 (22%)	Leukocytes / kg (?): 25 million	All patients	1996-2003
Ooi [30] (2004) N=21 (> 45y) Japan cord blood bank	28 months (median)	Age: 48 (45-53) Weight: 59 (44-76)	AML: 12 (57%) ALL: 1 (5%)	None: 0 1: 9 (43%) 2: 7 (33%) 3: 4 (19%)	Nucleated cells/kg: 25 million (range 16 – 37)	-	1999 – 2003
Ooi [31](2004) N=13 ALL Source of units: not specified	10 months (median)	Age: 36 (18-53) Weight: 56 (40-71)	ALL: 100%	2: 9 (69%)	Nucleated cells/kg: 29 million	-	2000 – 2003
Stevens[17] (Abstract) – 2004 / N=391 Sourc e of units: NY Blood Center	5 years	Age: > 40: 125 (32%) Weight: -	Leukemia: > 90%	-	-	-	1993 - 2003

Appendix 6 - Study Characteristics cont.

Observational studies / Year / Number of patients	Follow-up	Age (years) / Weight (kg) Median (range)	Underlying disease	HLA mismatch	Cell infusion (median)	Use of G-CSF / GM-CSF after transplantation	Period of inclusion of patients
Rocha[37] (2004) N=98 Source of units: Netcord	27 months	Age: 24.5 (15-55) Weight: 58 (38-92)	AML: 45 (46%) ALL: 53 (54%) Advanced phase: 51 (52%)	None: 6 (6%) 1: 48 (51%) 2: 37 (39%)	Nucleated cells/kg: 23 million (range 9-60)	-	1998 – 2002
Laughlin[38] (2004) / N=150 Source of units: NY Blood Center	40 months	Age > 31 yrs - 48% Weight: 68 (44-133)	AML: 58 (39%) ALL: 45 (30%) CML: 37 (25%) MDS: 10 (6%)	None: 0 1: 34 (23%) 2: 116 (77%)	Nucleated cells/kg: 22 (range 10-65)	-	1996 - 2001

ALL: acute lymphoid leukemia, AML: acute myeloid leukemia, CML: chronic myeloid leukemia, G-CSF: granulocyte colony stimulating factor, HLA: human leukocyte antigen, MDS: myelodysplastic syndrome

Appendix 6 cont. - Studies of Cord Blood Transplantation in adult patients (unrelated donors)
Study Results

Observational studies / Year / Number of patients	Overall survival	Transplantation-related mortality	Event-free survival	Disease-free survival	Leukemia / lymphoma relapses	Neutrophil recovery / Platelet recovery	Acute GVHD	Chronic GVHD
Sanz et al. [32] (2001) N=22 Source of units: several banks	-	100 days 43% (95% CI: 21% , 65%) Causes: Infection: 40% GVHD: 20% Hemorrhage:20% Secondary graft failure: 10% Conditioning treatment toxicity: 10%	-	Median f-up 8 months 12 (55%)	-	60 days 100% (among survivors) 2 patients died before engraftment Median time: 22 days	16/22 (73%) – grades II and higher	9/10 (90%) – patients at risk
Laughlin[34] (2001) N=68 Source of units: NY Blood Center	**100 days** 33 (49%) *Median f-up: 22 months* 19/68 (28%)	-	-	Median f-up 22 months 18 (26%)	1 year 4/54 (7.4%)	42 days 90% (85 , 100%) Median time: 27 days (range 13 , 59) 92% of survivors overall	31/55 (56%) – grades II and higher 100 days 60% (49 , 71%)	12/33 (36%) – patients who survived at least 100 days
Gluckman[35] (2001) N=108 Source of units: Netcord	**1 year** 27% (39% if leukemia in remission vs 17% more advanced)	-	-	-	-	60 days 81% Median time: 32 days (13-60days)	38% (grades II and higher)	-
Ooi [29](2004) N=18 (AML) Source of units: not specified	**2 years** 76.6%	-	-	-	3/17 (17%)	2 years 17/18 (94%)	11/17 (65%) (grades II and higher)	14/17 (82%) – evaluable patients

Appendix 6 - Study Results cont.

Observational studies / Year / Number of patients	Overall survival	Transplantation-related mortality	Event-free survival	Disease-free survival	Leukemia / lymphoma relapses	Neutrophil recovery / Platelet recovery	Acute GVHD	Chronic GVHD
Long[33] (2003) N=57 Source of units: several banks	90 days - 28 (50%) 3 years - 19% 2 years - 19% 1 year[a] - 25% [a] – 1 and 2 years estimates were extracted from figure 2B (article)	-	3 years 15%	-	-	42 days 49 (82%) Median time: 28 days *Platelet recovery* 19 (33%) Median time: 84 days	17 (30%) – grades II and higher Median time: 32 days (range 13-86)	8/25 (32%) – patients who survived longer than 100 days
Takahashi[36] (2004) N=68 Japan cord blood bank	Median f-up: 25 months 52 (76%)	1 year 9% (95% CI: 2% , 16%)	-	1 year 75%* (approximately)	1 year 15% * (approximately)	Neutrophil recovery 60 (88%) Median time: 22 days (range 16-41) Platelet recovery 55 (81%) Median time: 40 days (range 13-99)	30/60 (50%) – grades II and higher	42 (78%) – limited and extensive disease 13 (24%) – extensive disease Patients who survived 100 days
Ooi [30] (2004) N=21 (> 45y) Japan cord blood bank	Median f-up : 28 months 15 (71%)	-	-	2 years 71.4%	Median f-up: 28 months 4 (19%)	Neutrophil recovery 19 (90%) Median time: 22 days (range 18-32)	7 (37%) – grades II and higher	14 (88%) – limited and extensive 7 (44%) - extensive
Ooi [31](2004) N=13 ALL Source of units: not specified	Median f-up: 10 months 8 (62%)	-	-	Median f-up: 10 months 55.9%	-	*Neutrophil recovery* 11 (85%) Median time: 20 days (range 17-26) Platelet recovery 10 (77%) Median time: 48 days (range 40-106)	6 (55%) – grades II and higher	7 (88%) 1 (13%) - extensive
Stevens[17] (Abstract) – 2004 / N=391 Sourc e of units: NY Blood Center	1 year - 30.2% 5 years -23%							
Rocha [37](2004) N=98 Source of units: Netcord	2 years AML: 32% (95% CI: 25, 39) ALL: 34% (95% CI: 27,41) 1 year* - 40%	100 days* 38% 2 years 44%		2 years 36%.	2 years 24 (23%)	Neutrophil recovery 60 days 75% (95% CI: 66,84) Median time: 26 days (range 14-80)	Acute GVHD 26% (95% CI: 14,38) – grades II and higher 30% (95% CI: 20,40)	Chronic GVHD 18/61 (29.5%) (>100 days survivors) 2 years (cumulative)
Laughlin[38] (2004) / N=150 Source of units: NY Blood Center	3 years 26% (95% CI: 19 , 32)	63%	-	3 years 23% (95% CI:17,30)	26 (17%)	100 days 65% * Median time: 27 (95% CI: 25,29)	Acute GVHD 61 (41%)	Chronic GVHD 35/69 (51%) (>90 days survivors) Extensive - 33%

* Information derived from a graph

95% CI: 95% confidence interval, ALL: acute lymphoid leukemia, GVHD: graft-versus-host disease, TBI:total-body irradiation

Appendix 7 - Studies of Cord Blood Transplantation after non-myeloablative conditioning in adult patients

Study Characteristics

Observational studies / Year / Number of patients	Follow-up	Age / Weight	Underlying disease	HLA mismatch	Cell infusion (median)	Use of G-CSF / after transplantation	Period of inclusion of patients
Wagner (2004) – Abstract N=51	-	Age: 50 (range 19-60) Weight: -	-	Mostly 1-2 HLA mismatch	Nucleated cells 34 million/kg (range 11-57) 38 (75%) – received double units	-	-
Chao[73] (2004) N=13	20 months (median)	Age: 49 (range: 19-62) Weight: 65.7 (range: 42-99)	AML: 1 (8%) ALL: 3 (23%) CML: 1 (8%) Remainder are malignancies	None: 0 1: 3 (23%) 2: 10 (77%)	Nucleated cells 21 million/kg All patients received a single-unit transplant	-	2000 – 2003
Barker[74] (2003) N=21 First group of patients	-	Age: 49 (range 22-65) Weight: 75 (55-109)	AML: 10 (48%) ALL: 0 CML: 2 (9%)	-	-	-	2000-2001
Barker[74] (2003) N=23 2nd group (different conditioning regimen)	-	Age: 49 (range 24-58) Weight: 73 (range 51-119)	AML: 8 (36%) ALL: 3 (14%) CML: 2 (9%)	-	-	-	2000-2001
Miyakoshi[75] (2004) N=30	8 months (median)	Age: 59 (range 20-70) Weight: 52 (range 38-75)	AML: 14 (47%) ALL: 3 (10%) CML: 1 (3%)	None: 0 1: 6 (20%) 2: 24 (80%)	Nucleated cells 31 million/kg (range 20-43)	-	2002-2003

ALL: acute lymphoid leukemia, AML: acute myeloid leukemia, CML: chronic myeloid leukemia, G-CSF: granulocyte colony stimulating factor, HLA: human leukocyte antigen

Appendix 7 cont. - Studies of Cord Blood Transplantation after non-myeloablative conditioning in adult patients

Study Results

Observational studies / Year / Number of patients	Overall survival	Transplantation-related mortality	Event-free survival	Disease-free survival	Leukemia / lymphoma relapses	Neutrophil recovery / Platelet recovery	Acute / Chronic GVHD
Wagner (2004) – Abstract N=51	1 year 57% (95% CI:40 , 73)	180 days 18% (95% CI: 17,45)	-	-	1 year 31% (95% CI 17 , 45)	Neutrophil recovery 45 (90%) (95% CI: 82 , 98) Median time: 8 days (range 5-32)	Acute GVHD 27 (61%) (95% CI: 14,78) Chronic GVHD 1 year 36% (95% CI: 20 , 52)
Chao (2004) N=13	100 days - 77% 1 year - 43% 4 years - 22%	-	100 days - 69% 1 year - 43% 4 years - 24%	-	-	Neutrophil recovery 8 (67%) Median time: 12 days (range: 6-61)	Acute GVHD 2/5 (40%)
Chao[73] (2004) N=13	1 year 39% (95% CI: 23 , 56) Most frequent causes of death: infection, organ failure	100 days – 48% (95% CI: 26,70)	-	100 days 38% (95% CI: 17,59) 1 year 24% (95% CI: 6,42)	-	Neutrophil recovery 88% (95% CI: 72 , 100) Median time: 26 days (range 12-30) 2. graft failure: 11% Platelet recovery 24% (95% CI: 6 , 42)	Acute GVHD 44% (95% CI : 28,62) – grades II and higher Chronic GVHD 21% (95% CI: 8,34)
Barker[74] (2003) N=21 First group of patients	1 year 39% (95% CI: 23 , 56) Most frequent causes of death: infection, organ failure	100 days – 28% (95% CI: 10,46)	-	100 days 68% (95% CI: 48,88) 1 year 41% (95% CI : 15,76)	-	Neutrophil recovery 94% (95% CI: 84 , 100) Median time: 9.5 days (range 5-28) 2. graft failure: 0 Platelet recovery 80% (95% CI: 57 , 100)	Acute GVHD 44% (95% CI : 28,62) – grades II and higher Chronic GVHD 21% (95% CI: 8,34)
Barker[74] (2003) N=23 2nd group (different conditioning regimen)	1 year 32.7% (95% CI : 14 , 51)	100 days – 27% Regimen-related toxicity : 13%	1 year 22.2% (95% CI: 6 , 39)	-	-	Neutrophil recovery 26 (87%) (95% CI : 75 , 99) Median time : 18 (range 10-54) 2. graft failure: 0 Platelet recovery 16 (40%) (95% CI: 25 , 57) Median time: 39 days (range 25,95)	Acute GVHD 27% (95% CI: 11 , 43) – grades II and higher Chronic GVHD 3 (23%) – who survived > 100 days

95% CI: 95% confidence interval, GVHD: graft-versus-host disease

Appendix 8 – Studies of Cord Blood Transplantation in pediatric patients (unrelated donors)

Study Characteristics

Observational studies / Year / Number of patients	Age / Weight Median (range)	Underlying disease	HLA matching	Nucleated cell dose (million/kg): median	Period of patient inclusion
Wagner[67] (1995) N=44	Age: 4 (0.8-16) Weight: 18.6 (7.5 – 50)	Leukemia / lymphoma: 22 (50%)	None: 34 (77%) 1: 10 (23%)	-	1988 - 1994
Wagner[66] (1996) **N=18**	Age: 2.7 (0.1 – 21.3) Weight: 15.4 (3.3 – 78.8)	Leukemia: 13 (72%)	None: 7 (39%) 1-3: 11 (61%)	-	1994 – 1995
Michel[47] (2003) N=95	Age, yr (median): 6 (0.3 – 16) 22 (23%) had recvd stem cells before	Acute myeloid leukemia: 100%	None: 8 (9%) 1: 44 (47%) 2: 31 (33%) >=3: 10 (11%)	Nucleated cells: 44 (0.4 – 36) CD34+ ($x10^5$/kg): 1.38 (0.4 – 78)	1994-2002
Arcese[68] (1999) N=14	Age: 7.5 (2-16) Weight: 27.5 (11.5 – 66.5) Males: 8(57%)	All leukemia ALL: 11 (79%) AML: 2 (14%) CML: 1(7%)	None: 0 1: 12 (86%) 2: 2 (14%) Not higher mismatch by design	By design, > 15 million/kg (nucleated)	1995 - 1997
Barker[1] (2001) N=57 comparing with BMT – only results for UCBT are reported	Age: 4.5 (0.2-17.9) 5.8 (0.2 – 17.9) Weight: 19.6 (5-78) 20.2 (5-91)	Leukemia: 27 (47%)	None: 9 (16%) 1: 34 (60%) 2: 13 (23%) 3: 1 (2%)	Nucleated cell dose (millions/kg) 30 (10 – 280)	1994 - 1999
Locatelli [69](1998) N=54 Related and unrelated donors	Age: 5.5 (0.3 – 15) Weight: 20 (4.4 , 83)	All leukemia ALL: 70 (69%) AML: 32 (31%)	None: 36 (35%) – mainly with related donors 1:27 (27%) 2:25 (25%) 3: 11 (11%) 4: 2 (2%)	Nucleated cell dose (millions/kg) Related donors: 40 (7 , 100) Unrelated donors: 50 (15 , 465)	1990 – 1997
Rocha [42](2001) N=99 Comparative with BMT – only UCBT results are shown	Age: 6 (2.5 , 10) Weight: 21 (13 , 34)	All leukemia ALL: 65 (66%) AML: 30 (30%)	None: 8 (8%) 1: 43 (43%) 2: 40 (41%) 3: 6 (6%) 4: 1 (1%)	Nucleated cells infused (million/kg): 38 (24 , 360)	Published in 2001
Dalle[70] (2003) N=33 (Abstract)	-	-	-	Nucleated cells infused (million/kg) 37 (range 12-138)	1996 - 2002
Serra[84] (2000) N=28	Age : 6.5 (0.5-17) Weight : 25 (4-78)	Leukemia : 21 (75%)	None: 6 (21%) >=1: 22 (79%)	-	-

ALL: acute lymphoid leukemia, AML: acute myeloid leukemia, BMT: bone marrow transplantation, CML: chronic myeloid leukemia, G-CSF: granulocyte colony stimulating factor, HLA: human leukocyte antigen, UCBT: umbilical cord blood transplantation

Appendix 8 cont. – Studies of Cord Blood Transplantation in pediatric patients (unrelated donors)
Study Results

Observational studies / Year / Number of patients	**Overall Survival *(95% CI)***	**Event-free survival (95% CI)**	**Transplant-related mortality**	**Neutrophil recovery (95% CI)**	**Acute / Chronic GVHD (II-IV) (95% CI)**	**Leukemia relapse**
Wagner[67] (1995) N=44	Median f-up: 1.6 years 62% (47% , 77%)	Median f-up: 1.6 years 46% (22% , 69%)	-	*50 days* 82% (69% , 94%) Median time: 22 days (range 12-46)	Acute GVHD 100 days 3% (0 , 8%) Chronic GVHD 1 year 6% (0 , 15%)	-
Wagner[66] (1996) **N=18**	90 days 65% (41 , 89) 180 days 65% (41 , 89) 7 (39%): fungal infection 2(11%): chemot. toxicity 2(11%): relapse 1 (6%): GVHD IV	-	-	*60 days* *100% in patients surviving > 30d* 13 (72.2%) considering the 5 pts who died bef. Time (median): 24 (16 – 53)	100 days - 50% (24 , 76) – grades II-IV	90 days / 180 days 2/13 (15%) – 2 patients with AML in relapse at time of transplant
Michel[47] (2003) N=95	2 years 49% (39 , 59) infection: 19% relapse:24% GVHD: 3% Interst. Pneumonitis: 3% Organ failure: 2%	2 years 42% (32% , 52%)	100 days 20% (12 , 28)	*60 days* 78% (70 , 86) time (median): 26 days (12-57)	Acute GVHD 34 (36%) – grades II and higher 100 days - 35% (25 , 45) Chronic GVHD 2 years 15% (5% , 25%)	2 years 29% (19 , 39) de novo AML 29% (19 , 39) Sec. Leukemia 33% (-1 , 67)
Arcese[68] (1999) N=14	Median follow-up 18 m 9/14 (64%) acute GVHD: 2 (14%) sepsis: 1 (7%) progress. leukemia: 2(14%)	1 year 8 (57%)	3 (21%)	100% (Autologous reconst. in 3 (21%) despite high conditioning treat) Time (median): 33d	Acute GVHD 3/10 (30%) – grades II and higher Chronic GVHD - 3/8 (38%)	-
Barker[1] (2001) N=57 comparing with BMT – only results for UCBT are reported	*100 days* 73% (56% , 90%) 2 years 53% (31% , 75%)	-	-	45 days 49 (86%)	22 (39%)	6% (0 , 16%)
Locatelli [69](1998) N=54 Related and unrelated donors	*1 year* 42% (Kaplan Meyer)	2 years 34%	1 year 44%	60 days Unrelated donors: 79% Related donors: 84% (p=0.16)	Acute GVHD Unrelated donors: 37% Related donors: 41% (p=0.59)	2 years Unrelated donors: 40% Related donors: 42% (p=0.17) Children with high risk leukemia: 77% $\pm$ 14% Children with low risk leukemia: 31% $\pm$ 9%)

95% CI: 95% confidence interval, GVHD:graft-versus-host disease

Appendix 8 cont. – Studies of Cord Blood Transplantation in pediatric patients (unrelated donors)
Study Results

Observational studies / Year / Number of patients	Overall Survival (95% CI)	Event-free survival (95% CI)	Transplant-related mortality	Neutrophil recovery (95% CI)	Acute GVHD (II-IV) (95% CI	Chronic GVHD (95% CI)	Leukemia relapse
Rocha [42](2001) N=99 Comparative with BMT – only UCBT results are shown	*2 years* 35% (25 , 45)	2 years 31% (21% , 41%)	100 days 39% (29% , 48%)	60 days 80% (70% , 90%)	100 days 35% (24% , 45%)	2 years 25% (1% , 17%)	2 years 38% (25% , 53%)
Dalle[70] (2003) N=33 (Abstract)	3 years 62% (95%CI: 44% , 80%)	3 years 39.3% (95% CI: 15% , 63%)	100 days 25.8% (95% CI: 10% , 41%)	82% time (median):28 (range 22-49)	Acute GVHD 5 (19%) – grades II and higher Chronic GVHD 3 (11%) – none with extensive disease	-	
Serra[84] (2000) N=28	Median follow-up 16.6 months 10 (36%)	3 years 34.4% (95% CI:16.4% , 52.4%)	Median follow-up: 16.6 months 14 (50%)	21 (75%) time (median): 25 (range: 10-55)	Acute GVHD 18/21 (86%) - grades II and higher 5/18 (28%) – deaths due to acute GVHD Chronic GVHD: 0	-	

95% CI: 95% confidence interval, GVHD: graft-versus-host disease, UCBT: umbilical cord blood transplantation

Appendix 9 – Studies Comparing Cord Blood Transplantation and Bone Marrow/Peripheral Blood Transplantation

Study Characteristics

	Ooi et al.[41]		Rocha et al. (2001)[42]		Barker et al.[1]		Rodriguez-Marino et al.[43]		Frassoni et al.[44]		Rocha et al.[45] (2000) Sibling donors	
	UCBT (n=8)	**BMT (n=8)**	**UCBT (n=99)**	**BMT (n=262)**	**UCBT (n=26)**	**BMT (n=26)**	**UCBT (n=57)**	**BMT (n=53) matched**	**UCBT (n=12)**	**BMT (n=12)**	**UCBT (n=113)**	**BMT (n=2052)**
Age, median (range)	38.5 (21-51)	23 (17-36)	6 (2.5-10)	8 (5-12)	4.5 (0.2 – 17.9)	4.7 (0.6– 17.7)	7.1 (0.7-20.7)	9.2 (0.5-23)	5.3 (0.3-15)	7.3 (2.5-12.7)	5 (0-15)	8 (0-15)
Weight, median (range)	56.5 (46-80)	65.5 (41-84)	21 (13-34)	28 (20-42)	19.6 (5-78)	19.7 (5.9-80)	-	-	-	-	17 (5-46)	26 (4-109)
Diagnosis	AML 5(63%) ALL 3 (37%)	AML 3(37%) ALL 5 (63%)	AML – 4 (4%) ALL – 30 (30%)	AML – 18 (7%) ALL - 49 (19%)	AML – 5 (19%) ALL – 10 (38%)	AML – 5 (19%) ALL – 10 (38%)	AML: 17 (30%) ALL-23 (40%)	AML: 14(26%) ALL: 35 (66%)	AML: 1 (8%) ALL: 5 (42%)	AML: 3 (25%) ALL: 2 (17%)	Acute leukemia: 41 (36%)	Acute leukemia: 991 (48%)
Advanced disease	-	-	18 (18%)	52 (20%)	High risk – 15 (58%)	High risk – 15 (58%)	-	-	-	-	-	-
HLA mismatches	0- 0 1- 1(13%) 2- 5 (63%) 3- 2 (25%)	0-8 (100%)	0- 8 (8%) 1- 43 (43%) 2- 40 (41%) 3- 6 (6%) 4-1 (1%)	0- 211 (81%) 1- 46 (18%) 2- 1 (0.4%)	0 – 5 (19%) 1 – 12 (46%) 2 – 8 (31%) 3 – 1 (4%)	0 – 26 (100%)	-	-	Related and unrelated	Related and unrelated	Siblings 0 – 66 (62%)	Siblings 0 – 1122 (67%)
# cells infused Median (range)	-	-	Nucleated cells /kg ($x10^8$) 0.38 (0.24 – 3.6)	Nucleated cells /kg ($x10^8$) 4.2 (3.0 – 6.0)	Cell dose (millions/kg): 30 (10 – 280)	Cell dose (millions/kg) 200 (190 – 400)	-	-	Cell dose (millions/kg): 37 (19-180)	Cell dose (millions/kg) 500 (210-1260)	Nucleated cells (millions/kg) 47 (maximum 360)	Nucleated cells (millions/kg) 350 (maximum - 4100

ALL: acute lymphoid leukemia, AML: acute myeloid leukemia, BMT: bone marrow transplantation, HLA: human leukocyte antigen, UCBT: umbilical cord blood transplantation

Appendix 9 cont. – Studies Comparing Cord Blood Transplantation and Bone Marrow/Peripheral Blood Transplantation

Study Results

Endpoints	Ooi et al.[41]		Rocha et al. (2001)[42]		Barker et al.[1]		Rodriguez-Marino et al.[43]		Frassoni et al.[44]		Rocha et al.[45] (2000) Sibling donors	
	UCBT (n=8)	**BMT (n=8)**	**UCBT (n=99)**	**BMT (n=262)**	**UCBT (n=26)**	**BMT (n=26)**	**UCBT (n=57)**	**BMT (n=53) matched**	**UCBT (n=12)**	**BMT (n=12)**	**UCBT (n=113)**	**BMT (n=2052)**
Time to neutrophil recovery, median (range)	20 (18-25) p=0.0028	15 (14-21)	32 (11-56)	18 (10-40)	29 (2-54) p=0.03	22 (3-29)	-	-	22.5 (16-39) p=0.0002		26	18
Neutrophil recovery	-	-	60 days 80% (70 , 90) p=0.0004	60 days 96% (95 , 97)	45 days 88% p=0.41	45 days 96%	60 days 95% p=0.001	60 days 92%	-	-	60 days 89% (95 CI:82 , 94) p=<0.001 *RR: 0.40 (95% CI:0.32,0.51)	60 days 98% (95% CI: 97 , 99)
Platelet recovery	-	-	-	-	-	-	60 days 64% p=0.007	60 days 85%	-	-	180 days 86% (95% CI: 78,92) p<0.001	180 days 96% (95% CI: 94,97)
Acute GVHD (II-IV)	6 (75%)	5 (63%)	33 (33%) p=0.001	148 (56%)	42% p=0.8	35%	-	-	25% not significant	50%	14% (95% CI: 8,22) p=0.02	24% (95% CI: 22,26
Chronic GVHD		-	-	-	-	-	8/44 (18%) p=0.35	4/41 (10%)	0 not significant	2 (17%)	-	-
Relapse	1 (13%)	2 (25%)	2 years 38% (25 , 53) p=0.865	2 years 39% (32 , 46)	-	-	8 (14%) p=0.32	12 (23%)	-	-	-	-

BMT: bone marrow transplantation, GVHD: graft-versus-host disease, HLA: human leukocyte antigen, UCBT: umbilical cord blood transplantation

Appendix 9 cont. – Studies Comparing Cord Blood Transplantation and Bone Marrow/Peripheral Blood Transplantation

Study Results

Endpoints	Ooi et al.[41]		Rocha et al. (2001)[42]		Barker et al.[1]		Rodriguez-Marino et al.[43]		Frassoni et al.[44]		Rocha et al.[45] (2000) Sibling donors	
	UCBT (n=8)	**BMT (n=8)**	**UCBT (n=99)**	**BMT (n=262)**	**UCBT (n=26)**	**BMT (n=26)**	**UCBT (n=57)**	**BMT (n=53) matched**	**UCBT (n=12)**	**BMT (n=12)**	**UCBT (n=113)**	**BMT (n=2052)**
Survival	0	6 (75%)	2-year survival 36 (36%) p=0.01	2-year survival 129 (49%)	100 days survival 73% (56,90) p=0.35 2 years survival 53% (41, 75) p=0.4	100 days survival 85% (71 , 99) 2 years survival 41% (22 , 60)	100 days survival 44 (77%) p=0.65 1 year 57% 2 years - 3 years 50% p=0.56	100 days survival 43 (81%) 1 year 65% 2 years - 3 years 58%	-	-	100 days survival 86% (95% CI: 78 , 92) p=0.36 *RR : 1.15 (95% CI : 0.8,1.7) p=0.43	100 days survival 88% (95% CI : 87, 89)
Disease-free survival	2 years 85.7% p=0.51	2 years 75%			-	-	1 year 61% 2 years / 3 years 53% p=0.97	1 year 65% 2years / 3 years 57% / 54%	-	-	-	-
Event-free survival	-	-	2 years 31% (21 , 41) p=0.03	2 years 43% (37 , 49)	-	-	-	-	-	-	-	-
Early TRM	-	-	100 days 39% (29 , 48) p=0.0004	100 days 19% (14 , 24)	-	-	-	-	-	-	-	-

BMT: bone marrow transplantation, HLA: human leukocyte antigen, TRM= treatment-related mortality, UCBT: umbilical cord blood transplantation

* Relative risk with UCBT compared with BMT obtained in multivariate analyses

Appendix 9 – Studies Comparing Cord Blood Transplantation and Bone Marrow/Peripheral Blood Transplantation
Comparisons from multivariate analyses

Study	Neutrophil recovery	Platelet recovery (>20 x 10^9/L	GVHD	Overall mortality	Transplant-related mortality	Disease relapse	Disease-free survival
Takahashi[36] * (2004) N=113 (BMT=45 / UCBT=68)	0.18 (0.11 , 0.30)	0.48 (0.29 , 0.81)	Acute II-IV 0.61 (0.37 , 1.01) Acute III-IV 0.09 (0.01 , 0.58) Chronic (Extensive) 0.60 (0.28 , 1.28)	-	0.32 (0.12 , 0.86)	0.76 (0.16 , 3.56)	0.27 (0.14 , 0.51)
Laughlin[46] * (Abstract) – 2004 N=536 (BMT=367 / UCBT=169)	**Treatment failure** 1.56 (95% CI: 1.2 , 3)	-	Acute Similar (no HR is given) Chronic 1.97 (95% CI: 1.3 , 2.9)	1.63 (95% CI: 1.3 , 2.1)	2.09 (95% CI: 1.6 , 2.7)	-	-
Rocha[37] * (2004) (BMT=584 / UCBT=98)	0.49 (0.41 , 0.58)	-	Acute II-IV 0.57 (0.37 , 0.87) Chronic 0.64 (0.37 . 1.1)	1.05 (0.79 , 1.41)	1.13 (0.78 , 1.64)	1.02 (0.63 , 1.65)	1.05 (0.8 , 1.41)
Laughlin[38] * (2004) (BMT=367 (matched) / 83 (1 mismatch) / UCBT=150 (1-2 mismatches)	**Treatment failure** UCBT vs matched BMT 1.48 (1.18 , 1.86) UCBT vs BMT (1 mismatch) 0.94 (0.69 , 1.28)	-	-	UCBT vs matched BMT 1.53 (1.21 , 1.94) UCBT vs BMT (1 mismatch) 0.92 (0.68 , 1.26)	UCBT vs matched BMT 1.89 (1.45 , 2.48) UCBT vs BMT (1 mismatch) 0.99 (0.70 , 1.40)	UCBT vs matched BMT 0.73 (0.46 , 1.14) UCBT vs BMT (1 mismatch) 0.85 ((0.43 , 1.7)	-

BMT: bone marrow transplantation, GVHD: graft-versus-host disease, HLA: human leukocyte antigen, UCBT: umbilical cord blood transplantation
*Hazard ratio calculated using the Cox proportional hazard model [36 46 37 38] , results for cord blood compared to bone marrow transplantation [36 46 37 38].

Appendix 10 – Complications after Stem cell Transplantations

Publications identified in the peer-reviewed literature and that reported complications after stem cell transplantations are summarised below, and may include adult and pediatric patients who underwent bone marrow, peripheral blood or cord blood transplantation.

Information on GVHD, transplant-related mortality, and overall mortality has already been provided in session 5.2 and are therefore not included in this Appendix.

Infections

Infection is one of the most important causes of death in patients undergoing stem cell transplantations[35] [32], and it may be caused by immune deficiency due to the bone marrow ablation, or due to mucositis and alterations of skin barriers due to the conditioning regimen[85]. Infections may occur early or late (more than 100 days) after the transplantation, and its etiology may vary according to the period when it occurs as different factors are involved at different periods [85]. For instance, within 30 days of the transplantation or pre-engraftment period, neutropenia, mucositis, and acute GVHD are key factors predisposing the patients to infections, whereas 30-100 days after the transplantation (post-engraftment period), mucositis, acute GVHD, and impaired cellular immunity are the main risk factors for infections, and more than 100 days after the transplantation (late period), impaired cellular and humoral immunity and chronic GVHD are the main risk factors for the development of infections[85].

Outbreaks of bacterial, fungal, and viral infections in stem cell transplantation units have been reported in the literature, resulting in morbidity and mortality[86]. A report including 27 patients whom had undergone cord blood transplantation showed that 22(81%) of the patients had microbiologically documented infections, and 14(52%) had clinically documented infections within 100 days of the transplantation[39].

Cardiac complications

Moderate-to-severe cardiac complications may occur in 0-10% of the patients depending on the chemotherapy and conditioning regimens used, and also depending on the patient population[85].

Central Nervous System Complications

It is estimated that 11% to 44% of the patients undergoing allogeneic HSCT will develop central nervous system complications, such as cerebrovascular disease and infection, although this rate may be lower in patients undergoing non-myeloablative conditioning regimens[87].

Subdural hematomas are estimated to occur in 2.6%-12% of patients undergoing stem cell transplantations[85]. Intracranial hematomas are associated with a high risk of mortality, and may be caused by *Aspergillus* infection, cerebral venous sinus thromboses, and cyclosporine toxicity[85].

Gastrointestinal complications

Oral Mucositis

Oral mucositis is a complication associated with conditioning regimens used as a preparation to the stem cell transplantation[88]. It may occur early after the transplantation, and may increase the risk of infections and bleeding, interfere with the patient's ability to eat and speak, and in severe cases may require intubation of the patient due to airway obstruction [88].

A study reported that all patients receiving myeloablative conditioning regimens developed oral mucositis, half of which required parenteral opioid analgesia[85]. In a sample of 133 adult patients with chronic myeloid leukemia who underwent stem cell transplantation, 87 (65%) showed clinical signs of oral mucositis, while 36 (27%) presented with severe oral mucositis within less than 20 days after the transplantation[88].

Veno-occlusive disease

The conditioning regimen used in bone marrow/peripheral blood transplantations predisposes the patients to liver complications[89]. Severe veno-occlusive disease has been reported to occur in 4%-19% of the patients

undergoing a stem cell transplantation, starting within the first 21 days of the transplantation[85]. Among 1,652 patients who underwent bone marrow/peripheral blood transplantation, the reported incidence of veno-occlusive disease was 5.3% (95% confidence interval: 4.2% , 6.4%)[89].

Hemorrhagic cystitis

Factors such as chemotherapy and radiotherapy used in conditioning regimens, some virus (adenovirus, CMV, BK polyomavirus) may increase the risk of hemorrhagic cystitis[85].

One study reported a 30% (95% CI: 25% , 35%) cumulative incidence of hemorrhagic cystitis among 105 patients with acute lymphoid leukemia who underwent allogeneic stem cell transplantations[90]. Pediatric and adult patients were included, and transplantations were done from related and unrelated donors[90]. Hemorrhagic cystitis has different levels of severity ranging from microscopic hematuria, defined as grade I, to macroscopic hematuria requiring intervention (grade IV), and may result in prolonged hospitalisation and even death[90].

Malignancies

Malignancies developed after stem cell transplantation may be a consequence of chemotherapy and radiotherapy regimens [91]. One study reported cumulative incidences of new post-transplant malignancies of 1.7% (95% CI: 1.3 , 2.1) at 1 year and 6.9% (95% CI: 5.2 , 8.6) at 20 years[91]. Incidences of new solid tumours were 0.4% (95% CI: 0.2 , 0.6), and 3.8% (95% CI: 2.2 , 5.4) at 1 and 20 years respectively[91].

Among 262 patients who underwent autologous bone marrow/peripheral blood transplantation at one institution between 1982 and 1991 for non-Hodgkin's lymphoma, with myeloablative conditioning regimen consisting of cyclophosphamide and total-body irradiation, an overall incidence of myelodisplastic syndrome or acute myeloid leukemia was 7.6%, with a median time to onset of 31 months (range 10-101 months)[92]. Factors associated with an increased risk in univariate analyses were time between initial treatment and transplantation, longer exposure to chemotherapy and use of radiotherapy[92].

Neurologic complications

Neurologic complications following stem cell transplantations may be associated with infections, cerebrovascular or metabolic complications, chemotherapy or radiotherapy[93]. A study of 272 children undergoing autologous or allogeneic stem cell transplantation found a 13.6% incidence of neurologic symptoms within a median of 90 days after the transplantation (range 5 days – 8.8 years), including seizures, impairment of consciousness, motility and sensitivity disorders among others[93].

Peripheral nervous system complications

Complications such as poluneuropathies, Guillain-Barre syndrome-like disorders, polyomiositis (0.5%-3% allogeneic stem cell transplantations), and myasthenia may occur after stem cell transplantations and are may be associated with agents used in chemotherapy [85].

Pulmonary complications

Infectious or non-infectious pulmonary complications may occur in 40%-60% of the patients undergoing allogeneic stem cell transplantations, and may be responsible for 10-40% of the transplant-related deaths[94].

Idiopathic pneumonia syndrome (IPS), which is characterised as a diffuse lung injury for which no infectious cause has been identified, may occur in approximately 10% of patients undergoing allogeneic stem cell transplantations[85]. One of the factors that predispose patients to IPS is the conditioning regimen used before the stem cell transplantation[95]. A study observed a cumulative 8.4% incidence of IPS within the first 120 days among 917 patients who underwent bone marrow/peripheral blood transplantation following myeloablative conditioning regimen[95].

Common late pulmonary complications include bacterial, fungal, and viral infections, pulmonary edema, idiopathic pneumonia syndrome, bronchiolitis obliterans, and graft-versus-host disease[85].

Obstructive pulmonary disease was reported in 10.4% (median time: 184 days) out of a sample of 77 children who received allogeneic stem cell transplantation and who survived more than 100 days[71].

The use of radiotheraphy, chemotherapy and immunosupressive agents predisposes patients to non-infectious pulmonary complications occuring more than 100 days post-transplant[94]. Among 39 patients with

hematological malignancies who survived more than 3 months after an allogeneic stem cell transplantations from unrelated donors between 1997 and 2002 at one institution, the incidence of late-onset non-infectious pulmonary complications was 26%, with a median time to diagnoses of 8 months (range 3-11 months) [94].

Renal complications

Medications used during the stem cell transplantations may cause nephrotoxicity, and although it is estimated that the incidence of severe renal toxicity is rare, it is associated with a mortality of up to 80% if it occurs[85].

Avascular necrosis

Avascular necrosis is a possible complication of stem cell transplantation that may lead to joint destruction within 3-5 years, and often requiring surgical intervention[96]. Factors that may predispose patients to avascular necrosis are radiotherapy, corticosteroid use, age, and underlying disease[96]. A study on 207 patients who received autologous or allogeneic stem cell transplantation between 1991 and 2002 and who survived longer than 180 days showed a 5.8% incidence of avascular necrosis[96]. Another study found a 4-year cumulative incidence rate of avascular necrosis of 6.1% among 255 patients undergoing allogeneic stem cell transplantations [97].

Appendix 11 – Health Technology Assessment Reports

A report from the Alberta Heritage Foundation for Medical Research ("Cord Blood Transplantation – Technology Assessment report", 1998) was published in 1998, and presented a review of the results of the studies performed up to that year[21]. The authors concluded that the use of UCBT was a promising new technology but still in development, and that it might be an option for patients without a suitable BMT donor, especially children due to the small number of cells in the UCB unit[21]. However, the authors raised some issues associated with the published studies such as the fact that the majority of the published studies were small (18-562 patients), retrospective, with sometimes an overlap in the patients evaluated, and with an insufficient length of follow-up[21]. The authors believe that the lower number of cells present in the cord blood may result in a longer time for the recovery of the donors hematopoietic system when compared to BMT, but that UCBT may present some advantages over BMT, such as a lower incidence of GVHD[21], a complication that can be fatal. Nevertheless, in the authors opinion, due to the lack of adequate comparative studies between the two treatments, these questions could not be answered with the data available at the time[21].

A second report from the Alberta Heritage Foundation for Medical Research published in 2000 ("Allogeneic Stem Cell Transplantation Methods", 2000) presented a literature review on the three methods of stem cell transplantation, BMT, PBSCT, and UCBT, as well as the organization of services that perform stem cell transplantation, the transplantation activity in Canada, and the costs associated with the collection, processing, and transplantation of stem cells[8]. The report compared the three sources of stem cells with regards to safety, effectiveness, and costs[8]. The authors' conclusions were that UCBT has the highest safety among the three, due to a lower rate of donor and host infections[8]. Additionally, the authors believe that UCBT may result in a lower rate of GVHD, a better survival, but also in a longer time to hematopoietic recovery, although the results presented did not permit conclusions to be drawn[8]. In the authors' opinion, developments in stem cell transplantation techniques, including UCB, will help improve the number of patients requiring a transplant who will find a matched donor[8]. The authors compared the costs involved in the recruitment, collection, laboratory analyses, and transplantation between the three sources[8]. The authors used the same cost of the stem cell transplantation used, which is the focus of our report, for all 3 alternatives, C$ 140,000[8]. This cost included treatment and post-treatment costs, and considered that the patients would stay in the ICU for 50 days[8].

A report by the Technology Evaluation Center ("Transplanting Adult Patients with Hematopoietic Stem Cells from Placental and Umbilical Cord Blood", 2002), published in 2002, presented a review of the UCBT literature in adult patients, but no cost analysis was presented[50]. The authors concluded that, based on the available evidence, UCBT is an acceptable treatment for adult patients with life-threatening malignancies or bone-marrow disorders, for which there is an effective high dose regimen that requires stem cell transplantation, but for whom a donor with the same or a better HLA-matching characteristics is not available[50].

A technology assessment report by the Health Council of the Netherlands has been published in 2003 (Hematopoietic stem cells)[77]. Although the translation of the complete report to English was not possible, an executive summary in English was available. No information on the effectiveness, safety, or costs of UCBT is presented, but research on improvements in the number of cells in each unit, and on the immunological aspects of stem cells is encouraged in the report[77].

A technology assessment report from the Swedish Council on Technology Assessment in Health Care (SBU) published in 2001 could not be translated. According to the information presented in the summary, the authors concluded that the cost of each unit of UCB is similar to the cost of harvesting BM or PBSC from unrelated donors, however, neither cost or cost-effectiveness evaluations were found in the literature[48]. The authors also concluded that there was moderated scientific evidence on the efficacy and safety of UCBT available, and that therefore, at that point, UCBT should be considered as an experimental procedure[48].

The Norwegian Center for Health Technology Assessment has also prepared a report on the use of UCBT that was published in 2003[54]. Similarly to other reports, it could not be translated. As presented by the authors in the scientific summary, the literature suggests that the efficacy of UCBT is similar to that of BMT/PBSCT, on the other hand, in adults, due to the lower number of cells, the efficacy of UCBT seems to be lower than BMT/PBSCT in children[54]. The authors also believe that there are ethical questions still unanswered with regard to the storage, use, and proprietary rights to the cord blood[54].

The report from the Center for Technology Assessment *TA-Swiss* ("Human stemcells" TA 44, 2003) discussed the different sources of stem cells, but no formal effectiveness or cost analysis was presented[78].

The report from the Hayes Incorporated concluded that there is evidence in the literature about efficacy of UCBT in selected patients with life-threatening malignant and non-malignant diseases that affect the bone marrow/peripheral blood, however, the literature does not permit conclusions to be made regarding the comparison between UCBT and BMT/PBSCT[53].

The National Coordinating Centre for Health Technology Assessment[49] from the UK has published in 1998, a report entitled "Bone marrow and peripheral blood stem cell transplantation for malignancy". One review session on cord blood transplantation was included in the report, and according to the authors, further research was necessary at that point in order to confirm the efficacy of UCBT in the treatment of malignant and non-malignant diseases[49].

The Biological Response Modifiers Advisory Committee (BRMAC) of the Food and Drug Administration (FDA) has discussed the use of allogeneic HCS from unrelated donors obtained from UCB in a meeting in Februay 2003[52]. The discussion was based on the information on safety and efficacy of UCB used for hematopoietic reconstitution that had been provided to the FDA[52]. The conclusions reached were that UCBT is an acceptable therapy for different diseases, however, as the data available do not permit comparisons between the different sources of HSC, i.e., BM, PB, or UCB, the choice of the stem cell source should be made based on availability and medical judgement [52]. The committee considers that the data available on the three alternatives are very similar, except when the cell dose is lower or when there is a higher degree of HLA-mismatch between the host and the donor is larger[52]. Despite the difficulties in comparing the incidence of GVHD between UCBT and BMT due to inter-centre variability in the GVHD grading, the committee believes that the occurrence of GVHD after UCBT is not higher, and may even be lower than with BMT[52]. The committee also considers that it takes longer for the neutrophil and platelet recovery to occur following a UCBT compared to BMT, but, this does not seem to influence the overall survival, however, the data available suggest that engraftment is highly correlated with the cell dose infused[52]. The committee believes that although the CD34+ cell dose may predict the engraftment, information on the dose of total nucleated cells is enough for the decision-making[52].

Other recommendations included:

- The criteria for both obtaining UCB units, and reporting its results should be as strict as the ones used for obtaining BM donors[52];
- UCB transplants should be performed with a maximum of two HLA-mismatches between the host and the donor due to the limited information available on transplants with a greater degree of HLA-mismatch[52];
- The total nucleated cell dose in the UCB unit before thawing should be at least 25 x 10^6 /kg, with the requirement that the transplant centres recover at least 70% of the cells after thawing[52];
- No limit on age was set, however, the cell dose infused must be sufficient[52];
- The informed consent presented to the patient who will receive the transplant should included information on the cell dose[52];
- A certification program for the procedure used to thaw the unit at the transplant centre should be prepared[52];
- The FDA should demand the recording by the centres of the outcome information from the patients who received the transplant so that an assessment of its efficacy and quality assurance can be undertaken[52];
- The outcome variables recorded should included survival, disease-free survival, time to engraftment, time to hematopoietic recovery, immune reconstitition, and chimerism in experimental UCB studies[52];
- HLA typing should be repeated before the transplant, and this testing should also be done on a sample from a contiguously attached segment in order to avoid the transplantation between incompatible hosts and donors[52].

Appendix 12 – Health Benefits of stem cell transplantation

Health Benefits

In estimating the potential health benefits of extending the stem cell program, it will be assumed that stem cell transplantation will not be undertaken at the MUHC other than in individuals who are expected to succumb from the disease in the absence of such a procedure within an average period of nine months. It will also be assumed that overall survival following cord blood transplantation is comparable to survival following matched bone marrow.

To estimate the approximate number of lives that might be saved we first estimated the weighted average survival reported at 100 days, one, two, three and five years after cord blood transplantation reported in the literature, 49.5%[34 33], 32.5%[35 33 30,31 17,37], 31%[34 37], 24%[33,38], and 23%[17] respectively.

From 5 to 10 years survival can be predicted with reasonable confidence. In a follow-up of 1,715 leukemic patients (1059 allogeneic) who had survived two years after bone marrow transplantation, the chance of being in complete remission nine years following transplantation was 82%, regardless of the nature of leukemia, or the type of transplant[98]. Similarly, a study by Singhal et al., of 117 adult patients who survived the first 2 years after an allogeneic bone marrow transplantation from an identical sibling, found the probability of survival at 10 years was 81.2% [99]. For the purposes of this estimate we will therefore assume 80% survival at 10 years of those individuals who had already survived two years. With this assumption the overall survival at 10 years would be 25% (31% x0.8). **For the purpose of these estimations we will conservatively assume survival at 10 years to be 20% of those transplanted.** Thereafter, the absence of attrition from 5 to 10 years supports the view that "these patients have a higher probability of being cured, but the possibility of late relapse still remains"[98]. Assuming an average age transplant of 48, the average age of the 10-year survivors would be 58, with an average life expectancy of approximately 20 years (Quebec population life-expectancy, males, 1995-1997[100]). **For present purposes let us again, conservatively, assume an average survival for these individuals of half that time, 10 years.**

With the assumption that the average time of death is the midpoint of each of the above time intervals, the years of life that might result from 100 transplants would be as follows:

Table 2 – Years of life accumulated after 100 stem cell transplantations

Period	Individuals alive at the end of each period	Life-years accumulated in each period	Life-years accumulated discounted at 3%	Life-years accumulated discounted at 5%
Transplantation	100			
Transplantation to 100 days	50	20 years = ((50 patients*50 days) + (50 patients *100 days))/ 365	20	20
100 days to 1 year	33	30 years = ((17 patients*133 days) + (33 patients * 265 days)) / 365	30	30
1 year to 2 years	31	32 years = ((2 patients*180 days) + (31 patients* 365 days)) / 365	31.06	30.48
2 years to 3 years	24	28 years = ((7 patients * 180days) + (24 patients * 365 days)) / 365	26.39	25.4
3 years to 5 years	23	47 years = ((1 patient * 365) + (23 patients * 730 days)	42.40	39.65
5 years to 10 years	20	107 years	82.33	69.44
10 years to death	20	200 years= (20 patients x 10 years)	130.75	99.55
Total number life-years saved		**464 years**	**363**	**315**

Thus, based on the above assumptions, it is estimated that 100 transplantations would result in **at least 464 additional life years, 363 with 3% discounting, and 315 with 5% discounting.**

However, if transplantation had not been carried out these individuals would not have died immediately. The actual length of survival would obviously vary with many factors including the background pathology. The average survival of the mix of patients currently transplanted at the MUHC has been estimated to be approximately nine months (Dr. Pierre Laneuville, Personal communication). With this assumption, we must assume that in the absence of transplantation there would have been an accumulation of 75 years of life**. Thus, the net life years gained as a consequence of 100 transplantations would be (464 – 75) =389 life-years, or 288 at a discount rate of 3%, or 240 life-years at a discount rate of 5%.**

Quality of life of survivors

It can be assumed that, in the absence of transplantation, the quality of life of these individuals would on average be extremely poor.

Likewise, the average quality of life in the first year following the transplantation would also be poor to judge by the frequency of complications and relapses reported above. However, according to a study by Baker et al., 70% of the patients with chronic myeloid leukemia who survived for at least 2

years after an allogeneic bone marrow transplantation from an unrelated donor considered their overall health as good to excellent, although patients who developed chronic GVHD, approximately 38% of their sample, are 2.4 times more likely to rate their overall health as poor[58]. Messner et al. found that, while within the first 3 years after an allogeneic stem cell transplant (75% from related donors), patients who were long-term survivors showed decreases in stamina, ability to concentrate, and physical ability, after 3 years, the patients' quality of life was closer to the normal population [59].

Appendix 13 – Economic analysis stem cell transplantation

The published information on which to base estimates of the costs associated with stem cell transplantation is sparse. We have considered the costs associated with the transplantation procedure up to the time of hospital discharge, and the subsequent costs incurred during follow up separately.

Costs incurred from transplantation up to hospital discharge (excluding overhead and bone marrow/peripheral blood stem cells harvesting costs when possible)

Information concerning these costs is available in 5 published reports. Several others contained insufficient detail to be of use in making these estimates. In those that are published, the cost items covered and the final estimates varied considerably. Costs in other currencies were transformed into Canadian dollars with the following exchange rates: 1 US$ = 1.1860 CDN$ (Bank of Canada November 29th 2004). 1 Euro = 1.579 CDN$ (Bank of Canada Dec 2nd 2004).

An economic study of allogeneic transplantations performed in Canada has found a hospitalisation cost of CDN$37,354 and CDN$34,643 for bone marrow and peripheral blood stem cell transplantations from related donors respectively[28]. Costs after hospital discharge and within the first 100 days post-transplantation were CDN$8,729 and CDN$11,691 for bone marrow and peripheral blood transplantations respectively[28]. These costs are based on 20 patients who received bone marrow transplantation, and 10 patients who received peripheral blood stem cell transplantations[28].

A second Canadian report published in 2000 found a cost of CDN$140,000 for a hospitalisation for allogeneic stem cell transplantation regardless of the cell source,[8]. This cost was based on an assumption that patients hospitalised for a stem cell transplantation would spend 50 days in the intensive care unit (ICU) [8]. The overall median length of stay of 45 patients undergoing bone marrow transplantation at the MUHC during the years of 2000 and 2001 was 23 days (range: 15-132 days), during which time patients were not in the ICU but were in an isolated room and receiving nursing care.

According to the Alberta Health and Wellness Department, in 2003, the mean hospitalisation cost for a bone marrow transplantation was CDN$44,890 (standard deviation: 21,726)[55].

Table 3 shows the cost components of the hospitalisation for a stem cell transplantation at the MUHC. Physicians' fees were obtained from the Medical Specialists Manual of Régie de l'Assurance Maladie du Québec (RAMQ)[101], the other costs were obtained from the Finance department of the MUHC, Mr. Paul Tan.

Table 3 – Hospitalisation cost of an allogeneic stem cell transplantation at the MUHC (costs in Canadian dollars. Excludes overhead, bone marrow harvesting and donor costs

	Cost estimate at the MUHC Allogeneic peripheral blood stem cell transplantation (N=15)	**Cost estimate at the MUHC Allogeneic cord blood stem cell transplantation (N=2)**
Mean length of stay (days)	38	45
Staff (Transplant coordinator, nursing*)	$15,646	$18,528
Supplies	$1,191	$1,410
Pharmacy	$18,324	$18,324
Imaging and diagnostic tests	$989	$989
Laboratory	$1,582	$1,582
HLA matching	$753	$753
Stem cells laboratory (virology and microbiology tests, staff and supplies)	$1,823	$1,823
Hematologist fees	$1,835 (38 x $48.30§)	$2,070 (40 x $48.30 + 5 x $27.5)
Infectologist consultation fees	$77 ($95.40 x 81%)¶	$77 ($95.40 x 81%)¶
Total cost of an allogeneic stem cell transplantation at the MUHC	**$42,220**	**$45,556**

* Nursing costs were calculated assuming that in 85% of the time, the patients will require a ratio of 1 nurse for 3 patients, and in 15% of the time, the ratio would be 1:1.
§ $48.30 – RAMQ hematologist fee per day for the first 40 days of hospitalisation for a patient hospitalised in a short stay hospital, billing code 0094 / After day 40 = $27.50 – hematologist fee per day, billing code 0095 [101]
¶ $95.40 – RAMQ infectologist consultation fee including main visit and supplemental consultation fee for patients in a short stay, billing code 9160 [101]. We have assumed that 81% of the patients would need an infectologist consultation based on a publication by Saavedra et al. where 81% of the patients presented a microbiologically documented infection within the first 100 days of the transplantation[39].

The table 4 below shows the hospitalisation costs for bone marrow transplantation reported in these five publications, as well as the costs that will be assumed to pertain in the MUHC for the purpose of estimating economic impact.

The costs at the MUHC were estimated by the Finance Department and represents the mean hospitalisation costs based on resource utilization of 15 patients who underwent allogeneic stem cell transplantation from related donors, and 2 cord blood transplantations from unrelated donors in 2004 (overhead and bone marrow/peripheral blood harvesting costs were not included) [102].

Table 4 -Comparison of costs among BMT studies and the cost estimate at the MUHC with long-term follow-up (Costs in CDN$) – Excludes overhead, bone marrow harvesting and donor costs

	Uyl-de-Groot[79], 2001 (n=87)	Mishra[80], 2001 (N=17)	Agthoven[81], 2002 (N=29)	Couban[28], 1998 (N=20)	Alberta Health and Wellness[55] (N=255)	Cost estimate at the MUHC (Finance department)– Peripheral blood[102] (N=15)	Cost estimate at the MUHC (Finance department)– Cord blood[102] (n=2)
Base year for costs	1995	-	1998	1998	2003	2004	2004
Autologous/ Allogeneic	Allogeneic (adult, pediatric)	Allogeneic	Allogeneic – unrelated donors	Allogeneic	Mix	Allogeneic - related donors	Allogeneic - unrelated donors
Underlying disease	Acute Myeloid Leukemia	Leukemia, MDS	Acute leukemias	Leukemias and anemia	Mix	-	-
Mean age	< 65	40 (range 17-58)	35.6 (range 14-61)	-	-	-	-
Length of initial hospitalisation (days)	44	39	43	37	28.5	38	45
Medical professional fees included?	Yes	Yes	No	Yes	Yes	Yes	Yes
Total direct in-hospital)	**$41,800***	**$66,500****	**$39,200****	**$35,050**	**$34,475**	**$42,220§§**	**$45,556§§**
Follow-up costs (up to 100 days)	-	-	-	$8,729††	-	$9,914§	$9,914§
Follow-up costs to end of year 1	-	$12,100**	$61,600**	-	-	-	-
Follow-up costs To end of year 2	$21,600*	-	$78,400**	-	-	-	-

BMT = bone marrow transplantation / MDS = myelodysplastic syndrome

¶ - If the percentage of the total costs accounted for by overhead costs is not given in the article, we have **assumed** that overhead costs would represent 30% of the total costs

* Corresponds to the value given in the text and converted to Canadian dollars minus 20% for overhead costs

** Corresponds to the value given in the text and converted to Canadian dollars minus 30% which is the **assumed** proportion of overhead costs¶

§§ Details on table 3 above

†† Treatment costs included chemotherapy, radiation, drugs, parenteral nutrition, laboratory tests, nursing and hematologist fees, and medical consultations[28].

§ $8,729 was corrected for the inflation from 1998 until 2004, according to the rate of the Bank of Canada

As can be seen in the table above, the estimated direct costs of transplantation in these five reports vary from $34,475 to $66,500[28,55 79 80 81]. However, much of the disparity in these estimates may be due to differences in the per diem costs used. For example, the study conducted by Mishra et al. reported a mean per diem hospitalisation cost of $1,034, excluding overhead costs, with a mean length of hospitalisation of 39 days[80]. Nevertheless, it is likely that costs at the MUHC would be closer to the two Canadian estimates, ($35,050 and $34,475) than to the European estimates. **For the purpose of estimating the budget impact of expanding this technology we will assume that the costs of an allogeneic transplantation from an unrelated donor up to the time of hospital discharge would be $42,000 for**

bone marrow, and $45,500 for cord blood transplantations. We have **assumed** that the costs of an allogeneic transplantation would be similar between related and unrelated donor.

The cost of an umbilical cord blood unit for the hospital is $25,000 (Mr. Paul Tan, Finance department). We have assumed that a bone marrow/peripheral blood stem cell unit obtained from public banks would also have a cost of $25,000, as the literature estimates a cost of approximately $20,000-30,000[8]

Additional costs up to 100 days posttransplant. Couban and colleagues in a fairly recent Canadian study have estimated additional costs of $9,914 from the time of discharge up to100 days**. We will assume an additional cost of $10,000 at the MUHC to cover this time period.**

Long-term follow-up costs

The data on which to base estimates of the costs related to follow-up are extremely meagre. Nevertheless, in order to evaluate the budgetary impact an estimate of long-term follow-up cost must be attempted. Due to lack of long-term follow-up information with cord blood transplantations, we have assumed that the rates of complications and re-hospitalisations would be similar to the ones with bone marrow transplantations.

Table 5 presents the estimated costs of complications that may occur during the follow-up period.

Table 5 – Source for complications' costs during the follow-up period

Treatment	Unit cost	Source / Comments
Relapses	$4,169 Chemotherapy $2,165 – palliative care $95,500 – cord blood transplantation	Chemotherapy: CMG 736§, Alberta Health and Wellness [55] Palliative care: assuming that patients stayed in the hospital for 7 days. The cost was obtained by multiplying the average per diem cost in the medical wards, $264, plus $45 for hotel costs, by 7. Per diem costs provided by the Finance department of the MUHC for the financial year 2003-2004, Mr. Gilles Gaudet Stem cell transplantation assuming that patients would receive cord blood
Infection	$4,097	CMG 143 (pneumonia with pleurysis)§ assumed to be the closest to the cost of a hospitalisation for an infection– Alberta Health and Wellness [55]
Chronic GVHD	$3,228	According to Dr. Pierre Laneuville (Personal communication), patients receive immunosuppressive therapy on an outpatient basis and are seen at the hospital 3 times a week for approximately 3 months. Cost of ambulatory visit: - nursing cost of $11, 3/ week (15 minutes time of one nurse receiving $44/hour , Finance department MUHC), $ 396 / 90 days - Physician fee of $20, 3/ week (Regie de l'Assurance Maladie du Quebec, RAMQ, code 9129, hematology – control visit[103]) = $720 / 90 days - Medication costs: Cyclosporine PO 10mg/kg/day: $ 23.4 /day, $2,106 / 90 days (RAMQ – medication code 02242821[103]). Prednisolone PO 15mg: $0.066/day, $5.94 / 90 days (RAMQ - medication code 00312770[103])
Follow-up visits	$60	Cost of ambulatory visit: - Physician fee of $20 (Regie de l'Assurance Maladie du Quebec, RAMQ, code 9129, hematology – control visit[103]) - Nursing cost of $11 (15 minutes time of one nurse receiving $44/hour - Finance department MUHC). - Laboratory tests* $29 (Quality Management department)

*Laboratory tests include (white blood cells count, urinalysis, and blood chemistry tests), Dr. Pierre Laneuville (personal communication)

§ Hospitalisation costs include medication, medical and surgical supplies, salaries, administration personnel salaries, costs with patient care[55].

Table 6- ***Estimated follow-up costs after 100 days at the MUHC***

	Rate of event††	Estimated cost per event	Cost of event x rate of event	Cost with 3% discounting**	Cost with 5% discounting**
Relapses§					
Year 1	15%[36]	$12,564§	**$1,885** (12,564 x 15%)	**$1,885**	**$1,885**
Year 2	8% (23%(2-year)[37]-15%(year1)	$12,564§	**$1,005** (12,564 x 8%)	**$976**	**$957**
Years 3-10	1.6% (4.8% x 30% survivors)	$12,564§	**$201** (12,564 x 1.6%)	**$172**	**$156**
Infections					
100-180 days	14%[104]	$4,097	**$574** ($4,097 x 14%)	**$574**	**$574**
180 days – 1 year	3.5%[104]	$4,097	**$143** ($4,097 x 3.5%)	**$143**	**$143**
Year 2	9.3%[104]	$4,097	**$381** ($4,097 x 9.3%)	**$370**	**$363**
Years 3-9	8.1%[104]	$4,097	**$332** ($4,097 x 8.1%)	**$287**	**$260**
Patient follow-up costs‡					
100 days – 1 year	50% (survivors at 100 days)‡	$720	**$360** ($720 x 50%)	**$360**	**$360**
Year 2	33% (survivors at 1 year) ‡	$240	**$79** ($240 x 33%)	**$77**	**$75**
Chronic GVHD*					
Year 3 on	9.3% (30% x 31% (2-year survivors))*	$3,228	**$300 ($3,228 x 0.093)**	**$291**	**$285**

†† - Rates of events were obtained from published studies, for leukemia relapses and infections, the rates were obtained from studies on bone marrow transplantation, for chronic GVHD, rates from cord blood transplantation studies were obtained.

§ Treatment of relapses: 81% chemotherapy, 9% chemotherapy + 2nd transplantation, 10% palliative care (Dr. Pierre Laneuville, Personal communication). Estimated cost of relapses: **$12,564** = 81% x $4,169 (chemotherapy) + 9% x $99,669 (chemotherapy + transplantation) + 10% x 2,165 (palliative care). Additional cost details in table 5.

‡ **Assuming** that patients would be seen once a month during the first year, and once every 3 months in the second year[79]. Total cost of an ambulatory visit = $60. Additional cost details in table 5.

* According to information from Dr. Pierre Laneuville (personal communication), approximately 30% of the patients who survive at least 2 years would develop chronic GVHD, most of them mild. We have assumed that the chronic GVHD costs will incur on year 3. Additional cost details in table 5.

** Discounting was done assuming that the costs would be incurred halfway through the period, i.e., at 6 and 7 years for the periods 2-10 years and 2-9 years respectively.

Total costs of bone marrow and cord blood transplantations to the MUHC, from transplantation until 10 years of follow-up

Table 7 – Estimated costs of ***bone marrow transplantation*** per patient per year to the MUHC, excluding overhead and stem cell procurement costs

	Costs without discounting	Costs with discounting at 3%	Costs with discounting at 5%
Transplantation costs	$42,220	$42,220	$42,220
Costs from discharge until 100 days	$10,000	$10,000	$10,000
Other Year 1 Costs*	$2,962	$2,962	$2,962
Total year 1 costs	**$55,182**	**$55,182**	**$55,182**
Year 2 costs **	**$1,465**	**$1,423**	**$1,395**
Costs after year 2***	**$833**	**$750**	**$701**
Total cost from transplantation until 10 years	**$57,480**	**$57,355**	**$57,278**

* Costs with relapses, infections, and patient follow-up (table 6) / ** Costs with relapses, infections, patient follow-up (table 6) / *** Costs with relapses, infections and chronic GVHD (table 6)

Table 8 – Estimated costs of ***cord blood transplantation*** per patient per year to the MUHC, excluding overhead and stem cell procurement costs

	Costs without discounting	Costs with discounting at 3%	Costs with discounting at 5%
Transplantation costs	$45,556	$45,556	$45,556
Costs from discharge until 100 days	$10,000	$10,000	$10,000
Other Year 1 Costs*	$2,962	$2,962	$2,962
Total year 1 costs	**$58,518**	**$58,518**	**$58,518**
Year 2 costs **	**$1,465**	**$1,423**	**$1,395**
Costs after year 2***	**$833**	**$750**	**$701**
Total cost from transplantation until 10 years	**$60,816**	**$60,691**	**$60,614**

* Costs with relapses, infections, and patient follow-up

** Costs with relapses, infections, patient follow-up / *** Costs with relapses, infections and chronic GVHD

We have estimated that the total cost of an allogeneic stem cell transplantation including a 10-year follow-up (excluding the cost of procurement of stem cell) in an adult patient at the MUHC with 3% discounting would be approximately ***CDN$57,000 and CDN$60,500*** using bone marrow and cord blood respectively**.** We have assumed that the hospitalisation costs of an allogeneic bone marrow transplantation from an unrelated donor would be similar to the cost of transplantation from a related donor calculated at the MUHC.

According to the literature, the majority of the patients who survived up to 10 years can be considered cured[98], therefore, we considered the treatment costs of these patients would be negligible.

Acquisition cost of stem cells. The above estimate does not include the costs of searching for appropriately HLA matching donor cells, or their preparation, storage, and transportation. The acquisition cost of a cord blood stem cell unit at the hospital is $25,000 (Mr. Paul Tan, Finance department). We have assumed that the acquisition cost of a stem cell unit from bone marrow/peripheral blood from external banks would also be $25,000, as, according to the literature, the acquisition fee of a bone marrow/peripheral blood unit from an unrelated donor is approximately $20,000-$30,000[8]. However, while one unit of bone marrow cells is sufficient for one adult transplant procedure, because of a lower volume of stem cells in cord blood, on average two matched units are necessary for an adult transplantation (Dr. Pierre Lanueville, personal communication)**. Accordingly, we will assume the cost of stem cell acquisition to be $25,000 for each allogeneic bone marrow transplant, and $50,000 for each cord blood transplant.**

Assuming that the follow-up costs of cord blood transplantation would be similar to allogeneic bone marrow transplantation, the average total hospitalisation and post-discharge costs up to 10 years for stem cell transplantation from an unrelated donor would be CDN$82,000 ($57,000 + $25,000), the equivalent cost of using cord blood stem cells would be $110,500 ($60,500 + $50,000), as two stem cell units are used on average.

Budget impact

It is uncertain how many additional stem cell transplants can be expected in the coming years. In the year 2003, 10 cases were referred to another hospital and an unknown number are reported to have died because facilities were not available. Let us assume initially that if funds were made available in the coming year there would be a demand for 20 additional transplants, 10 using bone marrow stem cells and 10 using cord blood stem cells. Based on the annual cost per patient, reflected in tables 7 and 8 above, plus the cost of stem cell acquisition, without discounting, we arrive at the following estimates (excluding physicians' fees as they are not paid by the hospital):

Table 9 - ***Cumulative*** costs to the MUHC within the first 10 years posttransplantation of 20 additional allogeneic stem cell transplantations, 10 from bone marrow and 10 from cord blood (3% discounting):

	10 bone marrow transplantations/ year	10 cord blood transplantations/ year	Total cumulative cost / years
Year 1	$782,700	$1,063,710	$1,846,410
Year 2	$796,930	$1,077,940	$1,874,870
Year 10	$804,430	$1,085,440	$1,889,870

* Cost information from tables 3, 7-8 minus physicians' fees Includes stem cell units.

Appendix 14 – Cost per life year gained with allogeneic stem cell transplantations from unrelated donors

The cost per life year gained (LYG) with allogeneic stem cell transplantations (cord blood and bone marrow/peripheral blood) was calculated using the TreeAge Pro software (TreeAge Pro 2004 Suite, TreeAge Software Inc.). Separate calculations were performed for bone marrow and cord blood, with no discounting, 3% discounting and 5% discounting for both costs and outcomes.

Figure 5 shows an example of the decision tree used in the calculations. In this example the cost and life-years for a cord blood stem cell transplantation with no discounting is shown, however, the same calculation was repeated for bone marrow/peripheral blood transplantations with three levels of discounting (no discounting, 3% and 5%) in both cases. Tables 10 and 11 show the life-year and cost values used in the calculations.

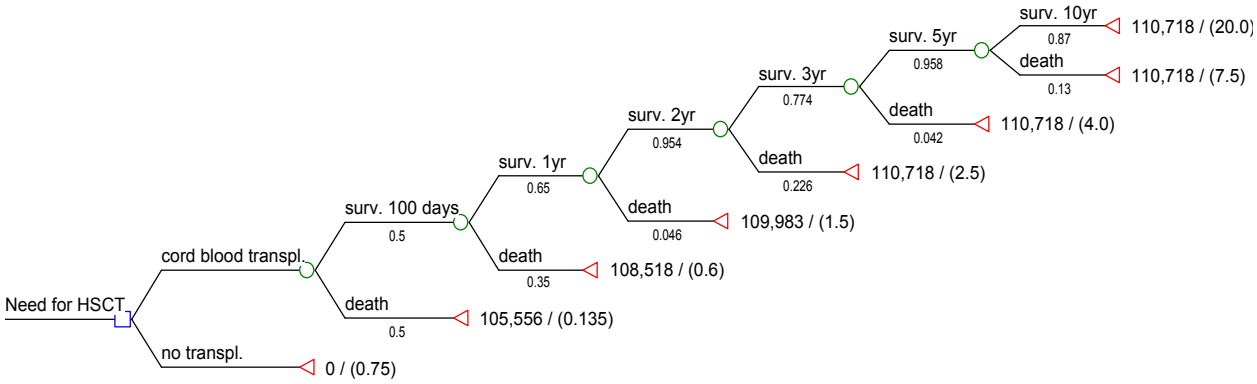


Figure 5 – Decision tree for cord blood transplantation, no discounting
Abbreviations used: HSCT=hematopoietic stem cell transplantation / surv=survival / transpl. = transplantation / yr=year
Values shown to the right of each triangular node represent the cost and the number of life years gained (in parentheses) respectively.

The survival probabilities in each interval are shown, cumulative survival rates are shown in table 10
Deaths were assumed to have occurred halfway through the period i.e., year 7.5 for the patients who died between years 5 and 10

If a patient does not undergo a stem cell transplantation, the survival is expected to be 9 months (0.75 years) (Appendix 12).

Table 10 – Cumulative survival rate and life-years per patient with cord blood and bone marrow/peripheral blood allogeneic transplantations used in the decision tree

	Survival rate in each interval	Cumulative survival rate	Cumulative life-years (no discounting)	Cumulative life-years (3% discounting)	Cumulative life-years (5% discounting)
100 days	0.5	0.50	0.27	0.27	0.27
Year 1	0.65	0.325	1	1	1
Year 2	0.954	0.31	2	1.97	1.95
Year 3	0.774	0.24	3	2.91	2.86
Year 5	0.958	0.23	5	4.71	4.55
Year 10	0.87	0.20	20*	15.32*	13.09*

* As described in Appendix 12, patients who survived to 10 years after the transplantation were assumed to have been alive for an additional 10 years
Survival rates were assumed to be similar for bone marrow/peripheral blood and cord blood transplantations as there was no clear evidence of a difference in the peer-reviewed literature.

Table 11 – Total costs for patients who underwent allogeneic bone marrow/peripheral blood and cord blood stem cells transplantations (Canadian dollars). Includes cost of stem cell units.

	BMT/PB costs (no discounting)	BMT/PB costs (3% discounting)	BMT/PB costs (5% discounting)	Cord blood (no discounting)	Cord blood (3% discounting)	Cord blood (5%discounting)
100 days	$77,220	$77,220	$77,220	$105,556	$105,556	$105,556
1 year	$80,182	$80,182	$80,182	$108,518	$108,518	$108,518
2 years	$81,647	$81,605	$81,577	$109,983	$109,941	$109,913
3 years	$82,480	$82,355	$82,278	$110,818	$110,691	$110,614
5 years	$82,480	$82,355	$82,278	$110,818	$110,691	$110,614
10 years	$82,480	$82,355	$82,278	$110,818	$110,691	$110,614

BMT= bone marrow / PB= peripheral blood
Cost calculations described in Appendix 13

Table 12 shows the expected costs per life-year gained with allogeneic bone marrow/peripheral blood and cord blood stem cell transplantations compared to no transplantation. Calculations performed using the decision tree illustrated in Figure 5.

Table 12 – Expected incremental cost, life-years and cost/LYG

Bone marrow / Peripheral blood transplants vs. no transplantation			
	No discounting	3% discounting	5% discounting
Incremental cost¶	$ 79,405	$79,365	$79,340
Incremental life-years§	3.89	2.94	2.47
Cost /LYG	**$20,413**	**$26,994**	**$32,121**
Cord Blood transplants vs. no transplantation			
	No discounting	3% discounting	5% discounting
Incremental cost¶	$ 107,741	$107,701	$107,676
Incremental life-years§	3.89	2.94	2.47
Cost /LYG	**$27,697**	**$36,633**	**$43,594**

§ Number of life years with stem cell transplantation minus 0.75 years, i.e., expected survival if the patient had not undergone stem cell transplantation
¶ Equals the cost of stem cell transplantation as we have assumed that the costs of a patient not undergoing stem cell transplantation would be zero
LYG=life-years gained

As shown in table 12 the cost / LYG compared to no transplantation is ***$26,994*** for bone marrow/peripheral blood and ***$36,633*** for cord blood.

Appendix 15 – Sensitivity Analyses

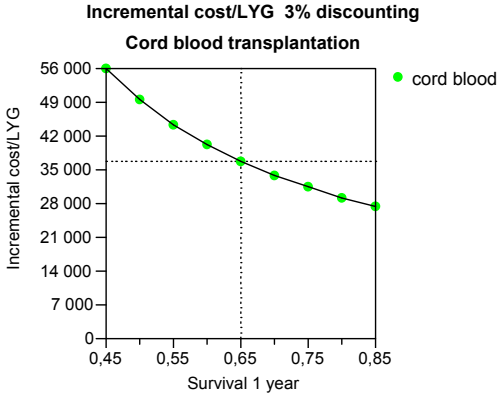
As patient characteristics may influence both the treatment costs and outcomes, we undertook the sensitivity analyses varying one or more variables at a time in order to test the consequences of these variations on the budget impact to the MUHC. The costs and outcomes with 3% discounting shown previously were used as the baseline for the sensitivity analyses. The sensitivity analyses were performed using the TreeAge Pro software (TreeAge Pro 2004 Suite, TreeAge Software Inc.).

Graphic results for cord blood transplantation with 3% discounting are shown, however, the same analyses were repeated for bone marrow/peripheral blood transplantation with 3% discounting, and the results are shown in the tables.

One-way sensitivity analyses

- Varying the transplantation and follow-up costs by 30% higher or lower. Stem cells unit procurement costs remained constant, as they would not be likely to change in the near future
- Varying the survival at different points by 30%

Figures 6 and 7 show the one-way sensitivity analyses varying the 1-year survival and 1-year cost of cord blood transplantation with 3% discounting. Table 13 shows the results for all one-way sensitivity analyses carried-out for bone marrow and cord blood transplantations.



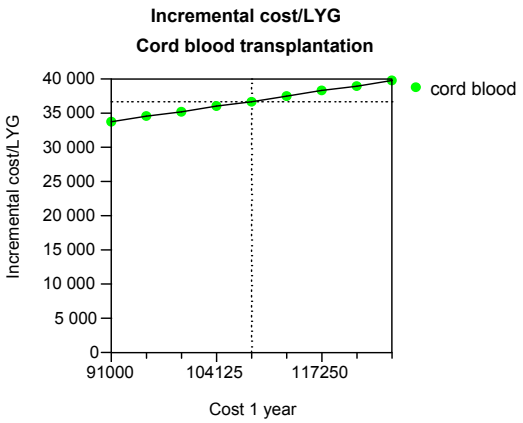


Figure 6 (left)– Sensitivitiy analysis, survival at 1 year (3% discounting). Values in the x axis represent the survival in the period between 100 days and 1 year. The dotted lines show the baseline result, i.e., survival rate 0.65 (=0.325 cumulative), $36,633/life-year gained
Figure 7 (right) - Sensitivitiy analysis, cost at 1 year (3% discounting). The dotted lines show the baseline results, i.e., cost=$108,518, cost/LYG= $36,633

Table 13 – Incremental cost/life-years gained variation in one-way sensitivity analyses (3% discounting)

Bone Marrow / Peripheral blood					
Survival at 1 year	0.85	0.75	**0.65 (baseline)**	0.55	0.45
Incremental cost/ LYG	$20,145 /LYG	$23,082 / LYG	**$26,994 / LYG**	$ 32,635/LYG	$41,193/ LYG
Survival at 5 years	1	0.97	**0,958**	0.81	0.67
Incremental cost/ LYG	$26,101 / LYG	$26,704/LYG	**$26,994 / LYG**	$31,005/LYG	$35,812/LYG
Survival 10 years	1	0.93	**0.87**	0.73	0.60
Incremental cost/ LYG	$24,876/LYG	$25,938/LYG	**$26,994 / LYG**	$29,746/LYG	$32,974/LYG
Cost at 1 year	$63,500	$71,875	**$80,182**	$88,625	$97,000
Incremental cost/ LYG	$24,193 / LYG	$25,619 / LYG	**$26,994/ LYG**	$28,472 / LYG	$29,898
Cord Blood					
Survival at 1 year	0.85	0.75	**0.65 (baseline**	0.55	0.45
Incremental cost/ LYG	$27,319 /LYG	$31,312 / LYG	**$36,633 / LYG**	$ 44,302/ LYG	$55,939 / LYG
Survival at 5 years	1	0.96	**0,958**	0.81	0.67
Incremental cost/ LYG	$35,420 / LYG	$36,662/LYG	**$36,633 / LYG**	$42,075/LYG	$48,599/LYG
Survival 10 years	1	0.93	**0.87**	0.73	0.60
Incremental cost/ LYG	$32,029/LYG	$35,198/LYG	**$36,633 / LYG**	$40,366/LYG	$44,747/LYG
Cost at 1 year	$91,000	$95,375	**$108,518**	$112,875	$126,000
Incremental cost/ LYG	$33,702 / LYG	$34,447 / LYG	**$36,633 / LYG**	$37,428 / LYG	$39,663

LYG=life-years gained

Multi-way sensitivity analyses

Multiway probabilistic sensitivity analyses were performed by simultaneously varying different parameters using Monte Carlo simulation, a technique that has been described in the literature[105].

With Monte Carlo simulation, instead of a single value, a distribution is assigned to each of the parameters being used in the sensitivity analysis[106]. The parameters used in the sensitivity analyses were survival at 1, 5 and 10 years, and cost at 1 year. A value is randomly drawn for each of these parameters from their specified distribution, and the expected cost and life-years of stem cells transplantation is then calculated[106]. This process is repeated several times[106] in order to produce a range of possible values for cost and life-years gained, in our case we chose 1,000 repetitions.

Table 14 shows the parameters selected for the sensitivity analyses, the distributions and ranges used. The triangular distribution was used for the cost and survival variables, as we did not have more specific knowledge of the shape of their distribution. With the triangular distribution the most likely and the extreme values of the parameter are assigned.

Table 14 – Values used in the multiway probabilistic sensitivity analysis

Variable	Distribution	Most likely value	Extremes
Survival 1 year	Triangular	0.65*	0.45 , 0.85
Suvival 5 years	Triangular	0.958*	0.67 , 1
Survival 10 years	Triangular	0.87*	0.60 , 1
1-year cost (bone marrow)	Triangular	$80,182**	$63,500 , 97,000
1-year cost (cord blood)	Triangular	$108,518**	$91,000 , 126,000

* The weighted average of the survival rates reported in the studies selected for the various intervals (Appendix 12) was used as the most likely values, and a 30% decrease and increase were used as the extreme values respectively. The survival rate in each interval are used in the table, cumulative rates are shown in table 10, Appendix 14.

** The cost of allogeneic stem cell transplantation estimated at the MUHC was used as the most likely value, and a 30% decrease and increase in the cost were used as the extreme values respectively. Stem cells unit procurement costs remained constant as they would not be likely to change in the near future.

As with the one-way sensitivity analyses, only part of the graphs are shown, however, the results for both cord blood and bone marrow/peripheral blood are described in the text. The costs and outcomes with 3% discounting were used as the baseline for the sensitivity analyses.

Figure 8 shows the distribution of the costs / LYG of ***cord blood vs. no transplantation*** using the Monte Carlo simulation. The results varied from $26,000 / LYG and $66,000 / LYG. Despite this wide range, it can be seen that in 71% of the time, the cost / LYG was between $30,000 and $45,000. With ***bone marrow/peripheral blood transplantations*** the cost per LYG varied from $20,000 and $59,000. In 80% of the time the cost/LYG was between $20,000 and $35,000.

Figure 9 shows the acceptability curve (right), which represents the proportion of the simulations in which the cost / LYG of ***cord blood vs. no transplantation*** is below a specific value[107]. It shows that in approximately 87% of the simulations the cost / LYG was $50,000 (vertical dotted line) or less. For ***bone marrow/peripheral blood***, in approximately 90% of the simulations the cost/LYG was $40,000 or less.

Figure 10 shows the 95% confidence interval of the incremental costs and life-years of ***cord blood vs. no transplantation***. In 95% of the simulations, the incremental costs varied from $98,196 to $111,838, LYG varied from 2.6 to 4.3, and the cost/LYG varied between $29,000 and $57,000.

Figure 11 shows the 95% confidence interval of the incremental costs and life-years of ***bone marrow/peripheral blood vs. no transplantation***. In 95% of the simulations, the incremental costs varied from $73,019 to $85,735, the LYG varied from 2.6 to 4.3, and the cost / LYG varied between $22,000 and $43,000.

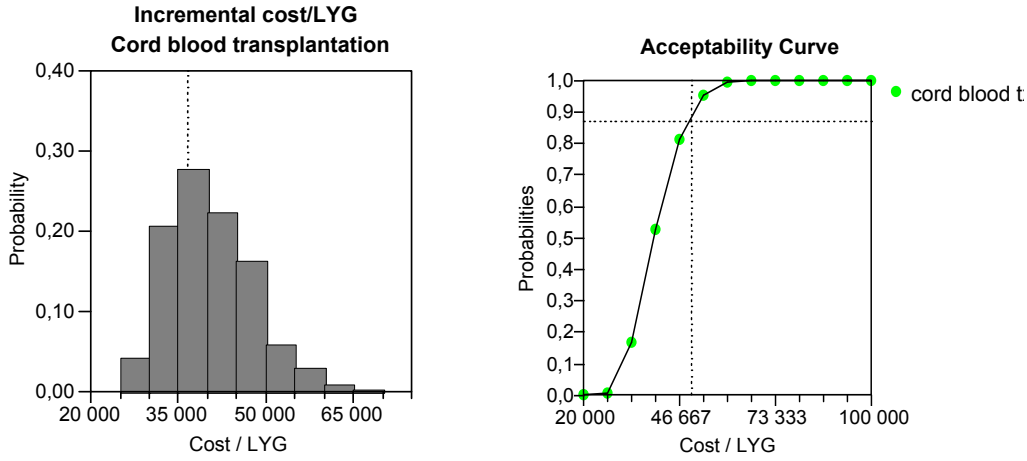


Figure 8 (left) - Distribution of the costs / life-year gained obtained using Monte Carlo simulation. The dotted line shows the expected results ($36,633, 3% discounting)
Figure 9 (right) - Acceptability curve, vertical dotted line at $50,000 / LYG, horizontal line at 87%

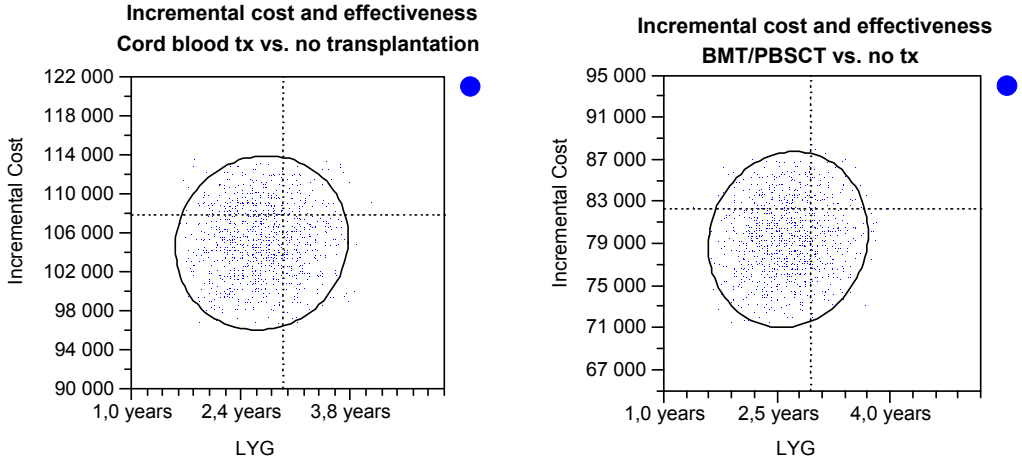


Figure 10 **(left)** – Incremental costs and LYG scatterplot. The circle shows the 95% confidence interval. The dotted lines show the expected baseline cost, $105,518 and LYG, 2.94 years
Figure 11 **(right)**– Incremental costs and LYG scatterplot. The circle shows the 95% confidence interval. The dotted lines show the expected baseline cost, $82,255 and LYG, 2.94 years. BMT=bone marrow transplantation/ PBSCT=peripheral blood stem cells transplantation

References

1. Barker JN, Davies SM, DeFor T, Ramsay NK, Weisdorf DJ, Wagner JE. Survival after transplantation of unrelated donor umbilical cord blood is comparable to that of human leukocyte antigen-matched unrelated donor bone marrow: results of a matched-pair analysis. Blood 2001; 97:2957-61.

2. Leger CS, Nevill TJ. Hematopoietic stem cell transplantation: a primer for the primary care physician. CMAJ 2004; 170:1569-77.

3. Surbek DV, Holzgreve W. [Stem cells from cord blood: current status and future potential]. Ther Umsch 2002; 59:577-82.

4. Ringden O. Allogeneic bone marrow transplantation for hematological malignancies--controversies and recent advances. Acta Oncol 1997; 36:549-64.

5. Lennard AL, Jackson GH. Stem cell transplantation. BMJ 2000; 321:433-7.

6. Grewal SS, Barker JN, Davies SM, Wagner JE. Unrelated donor hematopoietic cell transplantation: marrow or umbilical cord blood? Blood 2003; 101:4233-44.

7. Barker JN, Wagner JE. Umbilical cord blood transplantation: current state of the art. Curr Opin Oncol 2002; 14:160-4.

8. Alberta Heritage Foundation for Medical Research. Allogeneic stem cell transplantation methods. 2000; http://www.ahfmr.ab.ca/publications.html.

9. Rubinstein P, Stevens CE. Placental blood for bone marrow replacement: the New York Blood Center's program and clinical results. Baillieres Best Pract Res Clin Haematol 2000; 13:565-84.

10. Gluckman E, Locatelli F. Umbilical cord blood transplants. Curr Opin Hematol 2000; 7:353-7.

11. Rubinstein P, Carrier C, Scaradavou A, Kurtzberg J, Adamson J, Migliaccio AR, et al. Outcomes among 562 recipients of placental-blood transplants from unrelated donors. N Engl J Med 1998; 339:1565-77.

12. Gratwohl A, Baldomero H, Passweg J, Frassoni F, Niederwieser D, Schmitz N, et al. Hematopoietic stem cell transplantation for hematological malignancies in Europe. Leukemia 2003; 17:941-59.

13. Canadian Blood and Marrow Transplant Group. National and Québec Transplant Statistics. Accessed on 14/10/2004. Available to members only.

14. Kollman C, Abella E, Baitty RL, Beatty PG, Chakraborty R, Christiansen CL, et al. Assessment of optimal size and composition of the U.S. National Registry of hematopoietic stem cell donors. Transplantation 2004; 78:89-95.

15. Bone Marrow Donors Worldwide. Annual report 2003. http://www.bmdw.org/AnnualReport/BMDW2003.pdf . Last accessed - November 2003.

16. National Marrow Donor Program. Biennial Report of the National Bone Marrow Donor Registry - 2001 . http://www.marrow.org/NMDP/biennial_report_2001.html . Last accessed November 2004 .

17. Stevens Ce C, Scaradavou A, Rubinstein P. Cord blood transplantation to adult patients: A single-bank's experience. Biol Blood Marrow Transplant 2004; 10:733

18. Appelbaum FR. Allogeneic hematopoietic stem cell transplantation for acute leukemia. Semin Oncol 1997; 24:114-23.

19. Brenner MK. Cecil Textbook of Medicine. In: Anonymous 21st edition ed. 2000: W.B. Saunders Company, 988-991.

20. Weinberg K, Blazar BR, Wagner JE, Agura E, Hill BJ, Smogorzewska M, et al. Factors affecting thymic function after allogeneic hematopoietic stem cell transplantation. Blood 2001; 97:1458-66.

21. Alberta Heritage Foundation for Medical Research. Cord Blood Transplantation - Technology Assessment Report. 1998; HTA 13 ed. http://www.ahfmr.ab.ca/publications.html.

22. Food and Drug Administration - Department of Health and Human Services. 21 CFR Part 1271 - HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE–BASED PRODUCTS . 2001-2004; http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=1271&showFR=1.

23. Health Canada Directive. Technical requirements to address the safety of cells, tissues and organs for transplantation. 2003; http://www.hc-sc.gc.ca/hpfb-dgpsa/bgtd-dpbtg/cto_directive_e.pdf.

24. Warkentin PI. Voluntary accreditation of cellular therapies: Foundation for the Accreditation of Cellular Therapy (FACT). Cytotherapy 2003; 5:299-305.

25. Kvalheim G, Gratwohl A, Urbano-Ispizua A. JACIE accreditation in Europe moves ahead. Cytotherapy 2003; 5:306-8.

26. National Marrow Donor Program. A Medical Professional Guide to Unrelated Donors Stem Cell Transplantation. http://www.marrow.org/MEDICAL/medical_professionals_guide.pdf . Last accessed November 2004.

27. Osman K, Comenzo RL. Stem Cell Transplantation. Encyclopedia of Cancer, Second Edition 2002; 4:253

28. Couban S, Dranitsaris G, Andreou P, Price S, Tinker L, Foley R, et al. Clinical and economic analysis of allogeneic peripheral blood progenitor cell transplants: a Canadian perspective. Bone Marrow Transplant 1998; 22:1199-205.

29. Ooi J, Iseki T, Takahashi S, Tomonari A, Takasugi K, Shimohakamada Y, et al. Unrelated cord blood transplantation for adult patients with de novo acute myeloid leukemia. Blood 2004; 103:489-91.

30. Ooi J, Iseki T, Takahashi S, Tomonari A, Takasugi K, Uchiyama M, et al. Unrelated cord blood transplantation after myeloablative conditioning in patients over the age of 45 years. Br J Haematol 2004; 126:711-4.

31. Ooi J, Iseki T, Takahashi S, Tomonari A, Tojo A, Asano S. Unrelated cord blood transplantation for adult patients with acute lymphoblastic leukemia. Leukemia 2004; 18:1905-7.

32. Sanz GF, Saavedra S, Planelles D, Senent L, Cervera J, Barragan E, et al. Standardized, unrelated donor cord blood transplantation in adults with hematologic malignancies. Blood 2001; 98:2332-8.

33. Long GD, Laughlin M, Madan B, Kurtzberg J, Gasparetto C, Morris A, et al. Unrelated umbilical cord blood transplantation in adult patients. Biol Blood Marrow Transplant 2003; 9:772-80.

34. Laughlin MJ, Barker J, Bambach B, Koc ON, Rizzieri DA, Wagner JE, et al. Hematopoietic engraftment and survival in adult recipients of umbilical-cord blood from unrelated donors. N Engl J Med 2001;

344:1815-22.

35. Gluckman E, Rocha V, Chevret S. Results of unrelated umbilical cord blood hematopoietic stem cell transplant. Transfus Clin Biol 2001; 8:146-54.

36. Takahashi S, Iseki T, Ooi J, Tomonari A, Takasugi K, Shimohakamada Y, et al. Single-institute comparative analysis of unrelated bone marrow transplantation and cord blood transplantation for adult patients with hematological malignancies. Blood 2004;

37. Rocha V. Transplants of umbilical-cord blood or bone marrow from unrelated donors in adults with acute leukemia. New England Journal of Medicine 351:2276-2285.

38. Laughlin MJ. Outcomes after transplantation of cord blood or bone marrow from unrelated donors in adults with leukemia. New England Journal of Medicine 351:2265-2275.

39. Saavedra S, Sanz GF, Jarque I, Moscardo F, Jimenez C, Lorenzo I, et al. Early infections in adult patients undergoing unrelated donor cord blood transplantation. Bone Marrow Transplant 2002; 30:937-43.

40. Vose JM. Clinical Oncology. In: Anonymous 2nd ed. 2000:482-486.

41. Ooi J, Iseki T, Takahashi S, Tomonari A, Nagayama H, Ishii K, et al. A clinical comparison of unrelated cord blood transplantation and unrelated bone marrow transplantation for adult patients with acute leukaemia in complete remission. Br J Haematol 2002; 118:140-3.

42. Rocha V, Cornish J, Sievers EL, Filipovich A, Locatelli F, Peters C, et al. Comparison of outcomes of unrelated bone marrow and umbilical cord blood transplants in children with acute leukemia. Blood 2001; 97:2962-71.

43. Rodriguez-Marino S, Rademaker A, Kletzel M, Duerst R . Comparison of Outcomes after Transplantation of Unrelated Donor Umbilical Cord Blood versus matched sibling bone marrow for pediatric patients with leukemia and myelodysplastic syndromes. Biol Blood Marrow Transplant 2004; 10:12

44. Frassoni F, Podesta M, Maccario R, Giorgiani G, Rossi G, Zecca M, et al. Cord blood transplantation provides better reconstitution of hematopoietic reservoir compared with bone marrow transplantation. Blood 2003; 102:1138-41.

45. Rocha V, Wagner JE Jr, Sobocinski KA, Klein JP, Zhang MJ, Horowitz MM, et al. Graft-versus-host disease in children who have received a cord-blood or bone marrow transplant from an HLA-identical sibling. Eurocord and International Bone Marrow Transplant Registry Working Committee on Alternative Donor and Stem Cell Sources. N Engl J Med 2000; 342:1846-54.

46. Laughlin Mj M. Comparison of unrelated cord blood and unrelated bone marrow transplants for adults with leukemia a collaborative study: The New York blood center national cord blood program and The International bone marrow transplant registry. Biol Blood Marrow Transplant 2004; 10:734-5.

47. Michel G, Rocha V, Chevret S, Arcese W, Chan KW, Filipovich A, et al. Unrelated cord blood transplantation for childhood acute myeloid leukemia: a Eurocord Group analysis. Blood 2003; 102:4290-7.

48. The Swedish Council on Technology Assessment in Health Care. Transplantation of stem cells from umbilical cord blood. 2001; http://www.sbu.se/www/index.asp.

49. The NHS Health Technology Assessment Programme. Bone Marrow and Peripheral Blood Stem Cell Transplantation for Malignancy: a Review. 1998; Vol.2 No. 8 ed. http://www.hta.nhsweb.nhs.uk/ProjectData/3_project_record_published.asp?PjtId=963.

50. Technology Evaluation Center. Transplanting adult patients with hematopoietic stem cells from placental and umbilical cord blood. 2002; Vol.16 No. 17 ed.

51. Gratwohl A, Passweg J, Baldomero H, Horisberger B, Urbano-Ispizua A. Economics, health care systems and utilization of haematopoietic stem cell transplants in Europe. Br J Haematol 2002; 117:451-68.

52. Food and Drug Administration - Center for Biologics Evaluation and Research. Biological Response Modifiers Advisory Committee Summary Minutes. 2003; http://www.fda.gov/ohrms/dockets/ac/03/minutes/3924M1.htm . Last accessed - November 2004.

53. Hayes Medical Technology Report. Umbilical Cord Blood Stem Cell Transplantation. 2002;

54. The Norwegian Center for Health Technology Assessment. Use of hematopoietic stem cells from cord blood. 2003; http://www.kunnskapssenteret.no/smm/Publications/Engsmdrag/FramesetPublications.htm.

55. Alberta Health and Wellness. Health Costing in Alberta - 2003 Annual Report. http://www.health.gov.ab.ca/resources/publications/pdf/Health_Costing_2003.pdf.

56. Cohen Y, Nagler A. Cord blood biology and transplantation. Isr Med Assoc J 2004; 6:39-46.

57. Ballen K, Broxmeyer HE, McCullough J, Piaciabello W, Rebulla P, Verfaillie CM, et al. Current status of cord blood banking and transplantation in the United States and Europe. Biol Blood Marrow Transplant 2001; 7:635-45.

58. Baker KS, Gurney JG, Ness KK, Bhatia R, Forman SJ, Francisco L, et al. Late effects in survivors of chronic myeloid leukemia treated with hematopoietic cell transplantation: results from the Bone Marrow Transplant Survivor Study. Blood 2004; 104:1898-906.

59. Messner HA, Curtis JE, Lipton JL, Meharchand JM, Minden MD, Panzarella A. Three decades of allogeneic bone marrow transplants at the Princess Margaret Hospital. Clin Transpl 1999; 289-94.

60. Technology Assessment Unit - McGill University Health Centre. The Use of Implantable Cardiac Defibrillator (ICD) at the McGill University Health Centre (MUHC). http://upload.mcgill.ca/tau/icd.pdf . Last access:12/2005 2003;

61. Conseil d'évaluation des technologies de la santé du Québec. Rapport-CETS 98-3 RF. Hemodialyse et dialyse peritoneale: analyse comparative des rapports cout-efficacite. http://www.aetmis.gouv.qc.ca/fr/publications/scientifiques/autres/1998_03_res_fr.pdf Last access January 2005

62. Gluckman E. et al. Cord blood stem cell transplantation. Bailliere's Clinical Hematology 1999; 12:279-292.

63. Gluckman E, Rocha V, Boyer-Chammard A, Locatelli F, Arcese W, Pasquini R, et al. Outcome of cord-blood transplantation from related and unrelated donors. Eurocord Transplant Group and the European Blood and Marrow Transplantation Group. N Engl J Med 1997; 337:373-81.

64. Gluckman E, Rocha V, Arcese W, Michel G, Sanz G, Chan KW, et al. Factors associated with outcomes of unrelated cord blood transplant: guidelines for donor choice. Exp Hematol 2004; 32:397-407.

65. Isoyama K, Ohnuma K, Kato K, Takahashi TA, Kai S, Kato S, et al. Cord blood transplantation from unrelated donors: a preliminary report from the Japanese Cord Blood Bank Network. Leuk Lymphoma 2003; 44:429-38.

66. Wagner JE, Rosenthal J, Sweetman R, Shu XO, Davies SM, Ramsay NK, et al. Successful transplantation of HLA-matched and HLA-mismatched umbilical cord blood from unrelated donors: analysis of

engraftment and acute graft-versus-host disease. Blood 1996; 88:795-802.

67. Wagner JE, Kernan NA, Steinbuch M, Broxmeyer HE, Gluckman E. Allogeneic sibling umbilical-cord-blood transplantation in children with malignant and non-malignant disease. Lancet 1995; 346:214-9.

68. Arcese W, Guglielmi C, Iori AP, Screnci M, Carmini D, Testi AM, et al. Umbilical cord blood transplant from unrelated HLA-mismatched donors in children with high risk leukemia. Bone Marrow Transplant 1999; 23:549-54.

69. Locatelli F, Rocha V, Chastang C, Arcese W, Michel G, Abecasis M, et al. Factors associated with outcome after cord blood transplantation in children with acute leukemia. Eurocord-Cord Blood Transplant Group. Blood 1999; 93:3662-71.

70. Dalle J, Duval M, MA, Rousseau P, Wagner Eea. Comparative outcome of unrelated hematopoietic stem cell transplantation (HSCT) with cord blood (CB) vs Bone marrow (BM) in pediatric recipients. Biol Blood Marrow Transplant 2003; 9:78-79.

71. Alonso Riofrio R, Villa Asensi JR, Sequeiros Gonzalez A, Diaz Perez MA, Gonzalez Vicent M, Madero Lopez L. [Obstructive lung disease after allogenic stem cell transplantation in children]. An Pediatr (Barc) 2004; 61:124-30.

72. Wagner JE. et al. Umbilical cord blood transplantation after a non-myeloablative therapy in high risk adults. Biology of Blood and Marrow Transplantation 2004; 10:733-734. Abstract.

73. Chao NJ, Koh LP, Long GD, Gasparetto C, Horwitz M, Morris A, et al. Adult recipients of umbilical cord blood transplants after nonmyeloablative preparative regimens. Biol Blood Marrow Transplant 2004; 10:569-75.

74. Barker JN, Weisdorf DJ, DeFor TE, Blazar BR, Miller JS, Wagner JE. Rapid and complete donor chimerism in adult recipients of unrelated donor umbilical cord blood transplantation after reduced-intensity conditioning. Blood 2003; 102:1915-9.

75. Miyakoshi S, Yuji K, Kami M, Kusumi E, Kishi Y, Kobayashi K, et al. Successful engraftment after reduced-intensity umbilical cord blood transplantation for adult patients with advanced hematological diseases. Clin Cancer Res 2004; 10:3586-92.

76. Australian Health Technology Advisory Committee. Superspecialty service guidelines for hematopoietic stem cell transplantation. 1999;

77. Gezondheitsraad Health Council of the Netherlands . Hematopoietic Stem Cells. 2003;

78. Centre for Technology Asessment - TA Swiss. Human stem cells. 2003; TA-44/2003 ed. http://www.ta-swiss.ch/www-support/reportlists/publicationslifesciences_d.htm.

79. Uyl-de Groot CA. Costs of diagnosis, treatment, and follow up of patients with acute myeloid leukemia in the Netherlands. Journal of Hematotherapy & Stem Cell Research 2001; 10:187-192.

80. Mishra V, Vaaler S, Brinch L. A prospective cost evaluation related to allogeneic haemopoietic stem cell transplantation including pretransplant procedures, transplantation and 1 year follow-up procedures. Bone Marrow Transplant 2001; 28:1111-6.

81. van Agthoven M, Groot MT, Verdonck LF, Lowenberg B, Schattenberg AV, Oudshoorn M, et al. Cost analysis of HLA-identical sibling and voluntary unrelated allogeneic bone marrow and peripheral blood stem cell transplantation in adults with acute myelocytic leukaemia or acute lymphoblastic

leukaemia. Bone Marrow Transplant 2002; 30:243-51.

82. Jacobs P, Hailey D, Turner R, MacLean N. Allogeneic stem cell transplantation. An economic comparison of bone marrow, peripheral blood, and cord blood technologies. Int J Technol Assess Health Care 2000; 16:874-84.

83. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant 1995; 15:825-8.

84. Badell Serra I, Olive Oliveras T, Madero Lopez L, Munoz Villa A, Martinez Rubio A, Verdeguer Miralles A, et al. [Transplantation of umbilical cord blood hematopoietic progenitor cells in children]. An Esp Pediatr 2000; 53:513-9.

85. Pallera AM, Schwartzberg LS. Managing the toxicity of hematopoietic stem cell transplant. J Support Oncol 2004; 2:223-37; discussion 237-8, 241, 246-7.

86. McCann S, Byrne JL, Rovira M, Shaw P, Ribaud P, Sica S, et al. Outbreaks of infectious diseases in stem cell transplant units: a silent cause of death for patients and transplant programmes. Bone Marrow Transplant 2004; 33:519-29.

87. Kishi Y, Miyakoshi S, Kami M, Ikeda M, Katayama Y, Murashige N, et al. Early central nervous system complications after reduced-intensity stem cell transplantation. Biol Blood Marrow Transplant 2004; 10:561-8.

88. Robien K, Schubert MM, Bruemmer B, Lloid ME, Potter JD, Ulrich CM. Predictors of oral mucositis in patients receiving hematopoietic cell transplants for chronic myelogenous leukemia. J Clin Oncol 2004; 22:1268-75.

89. Carreras E, Bertz H, Arcese W, Vernant JP, Tomas JF, Hagglund H, et al. Incidence and outcome of hepatic veno-occlusive disease after blood or marrow transplantation: a prospective cohort study of the European Group for Blood and Marrow Transplantation. European Group for Blood and Marrow Transplantation Chronic Leukemia Working Party. Blood 1998; 92:3599-604.

90. El-Zimaity M, Saliba R, Chan K, Shahjahan M, Carrasco A, Khorshid O, et al. Hemorrhagic cystitis after allogeneic hematopoietic stem cell transplantation: donor type matters. Blood 2004; 103:4674-80.

91. Baker KS, DeFor TE, Burns LJ, Ramsay NK, Neglia JP, Robison LL. New malignancies after blood or marrow stem-cell transplantation in children and adults: incidence and risk factors. J Clin Oncol 2003; 21:1352-8.

92. Stone RM, Neuberg D, Soiffer R, Takvorian T, Whelan M, Rabinowe SN, et al. Myelodysplastic syndrome as a late complication following autologous bone marrow transplantation for non-Hodgkin's lymphoma. J Clin Oncol 1994; 12:2535-42.

93. Faraci M, Lanino E, Dini G, Fondelli MP, Morreale G, Dallorso S, et al. Severe neurologic complications after hematopoietic stem cell transplantation in children. Neurology 2002; 59:1895-904.

94. Patriarca F, Skert C, Sperotto A, Damiani D, Cerno M, Geromin A, et al. Incidence, outcome, and risk factors of late-onset noninfectious pulmonary complications after unrelated donor stem cell transplantation. Bone Marrow Transplant 2004; 33:751-8.

95. Fukuda T, Hackman RC, Guthrie KA, Sandmaier BM, Boeckh M, Maris MB, et al. Risks and outcomes of idiopathic pneumonia syndrome after nonmyeloablative and conventional conditioning regimens for allogeneic hematopoietic stem cell transplantation. Blood 2003; 102:2777-85.

96. Tauchmanova L, De Rosa G, Serio B, Fazioli F, Mainolfi C, Lombardi G, et al. Avascular necrosis in long-term survivors after allogeneic or autologous stem cell transplantation: a single center experience and a review. Cancer 2003; 97:2453-61.

97. Schulte CM, Beelen DW. Avascular osteonecrosis after allogeneic hematopoietic stem-cell transplantation: diagnosis and gender matter. Transplantation 2004; 78:1055-63.

98. Frassoni F, Labopin M, Gluckman E, Prentice HG, Gahrton G, Mandelli F, et al. Are patients with acute leukaemia, alive and well 2 years post bone marrow transplantation cured? A European survey. Acute Leukaemia Working Party of the European Group for Bone Marrow Transplantation (EBMT). Leukemia 1994; 8:924-8.

99. Singhal S, Powles R, Treleaven J, Kulkarni S, Horton C, Mehta J. Long-term outcome of adult acute leukemia patients who are alive and well two years after allogeneic bone marrow transplantation from an HLA-identical sibling. Leuk Lymphoma 1999; 34:287-94.

100. Health Canada. Life tables, Canada, Provinces and Territories 1995 - 1997. *http://www.statcan.ca:8096/bsolc/english/bsolc?catno=84-537-X* Last access January 2005

101. Régie de l'Assurance Maladie du Québec. Tarification de Visites, Médecins spécialists. http://www.ramq.gouv.qc.ca/fr/professionnels/manuels/150/012_b_tarif_visites_acte_spec.pdf . Last access December 2004

102. McGill University Health Centre - Finance Department. Analysis for Stem Cells Transplant Program.

103. Régie de l'Assurance Maladie du Quebec. Liste de medicaments assures. http://www.ramq.gouv.qc.ca/fr/professionnels/listmed/lm_tdmf_ajour.shtml. Last access 17/DEC/2004

104. Robin M, Guardiola P, Dombret H, Baruchel A, Esperou H, Ribaud P, et al. Allogeneic bone marrow transplantation for acute myeloblastic leukaemia in remission: risk factors for long-term morbidity and mortality. Bone Marrow Transplant 2003; 31:877-87.

105. Critchfield GC, Willard KE, Connelly DP. Probabilistic sensitivity analysis methods for general decision models. Comput Biomed Res 1986; 19:254-65.

106. Doubilet P, Begg CB, Weinstein MC, Braun P, McNeil BJ. Probabilistic sensitivity analysis using Monte Carlo simulation. A practical approach. Med Decis Making 1985; 5:157-77.

107. Lothgren M, Zethraeus N. Definition, interpretation and calculation of cost-effectiveness acceptability curves. Health Econ 2000; 9:623-30.