

Appendix

Pediatric bone marrow donation and the potential risks/benefits of G-CSF administration to the donor.

Introduction

This COG consensus document was prepared as part of a dialog with the COG Ethics Committee about the use of G-CSF in minor donors as part of their bone marrow donation for a sibling. The essential conclusion of the data presented here is that there is an enormous experience with the use of G-CSF long term in children without malignant disorders, and there is also experience with the use of G-CSF in tens of thousands of normal adult stem cell donors. We feel that these data clearly address both of the central concerns raised by the ethics committee: 1) the potential leukemia risk posed by short-term G-CSF administration, and 2) availability of adult data.

In sibling bone marrow donation, there are direct benefits to the donor. The main issue with this trial is whether the additive risk of 4 days of G-CSF administration to the donor is justified. Potential benefits of G-CSF stimulated bone marrow (G-BM) to the recipient are more rapid recovery post transplant and potentially less chronic GVHD. There is also potential benefit for the G-CSF treatment for the donor, if it is confirmed to be equivalent or better than bone marrow, in that smaller harvests may allow for decreased risk of donor transfusion and less post donation anemia. This is frequently an issue in pediatrics where the donor may be much smaller than the recipient. The main benefit to the donor, however, would be improved likelihood of survival and less suffering for their sibling.

This benefit needs to be balanced against the risk of 4 days of G-CSF administration. The pediatric pilot for this trial (PBMTCT SCT0233) is nearing completion and addresses the more easily defined and measurable assessments of donor risk (pain, ability to collect sufficient cells, engraftment kinetics). The theoretical risks of leukemogenesis and the rare event risk of serious adverse event (e.g. worsening of an underlying autoimmune process, splenic rupture) are not fully definable and will not be able to be addressed with any statistical rigor in a trial of this size. However, based on the COG Ethics committee comments and those discussed at a recent NIH sponsored meeting on Donor Safety, the trial will include two aspects to address donor safety: recording of short-term donor adverse effects and a plan for long term follow-up of healthy donors on both the bone marrow and G-BM arms. This experience will contribute additively to other large trials of G-CSF administration to healthy donors and over the next decades these important questions will be answerable.

It is critical that randomized clinical trials in SCT be performed to avoid the empiric adoption of new treatments without the appropriate scientific rigor. The proposed trial is a randomized phase III trial that will evaluate the impact of G-CSF stimulation on outcome from matched sibling donor transplantation for acute leukemia. The issues in pediatrics are unique and require that the study be performed in children.

In this document we will review a) the known and potential benefits to the BMT recipient receiving a G-CSF stimulated BM (G-BM) graft compared to stem cells (G-PB) or conventional (unstimulated) BM and b) the known and potential risk to the recipient with short course G-CSF.

Ethical background for minor sibling donation in BMT

There are currently three methods of hematopoietic stem cell collection used in pediatric transplantation: 1) conventional BM collected by needle aspiration, 2) PBSC collected after G-CSF stimulation by apheresis and 3) BM collected after G-CSF stimulation by needle aspiration. Regardless of the method chosen there are

risks to the donor. This results in a unique ethical situation, where a minor sibling who is unable to consent to a harvest procedure undergoes such a procedure with parental consent. In the early days of allogeneic bone marrow transplantation, BM harvest on minor siblings was controversial because there was concern that the procedure would pose no benefit to the unaffected sibling.

However, over the past 25 years a worldwide consensus has developed that has allowed use of operative BM harvest in minor siblings of patients requiring BMT. Undergoing BM or PBSC transplantation is the only or most likely curative option for patients who require the procedure. Stem cells obtained from a sibling provide a greater chance for a cure and a lower risk of toxicity than stem cells obtained from a matched unrelated adult donor. Balancing the risk to the donor, is the substantial benefit to the donor in: 1) not experiencing the death of a sibling, 2) not experiencing the risk of psychological trauma and post-traumatic stress disorder (44, 45), associated with the death of a sibling and 3) not experiencing the profound effect on their parent or parents that would accompany the death of their sibling. Thus, use of BM from a normal sibling donor, where available, is standard of care. BM from an unrelated adult donor is utilized only when matched sibling donors are not available. Indeed, there are several clinical situations (AML in first CR is one such example), where a BMT is undertaken only when a matched sibling donor is available. Any use of stem cell collection from a normal sibling donor must fit in to this essential ethical framework. Attempts to improve transplant outcome improve the likelihood of benefit to the donor. The proposed study very clearly fits into this framework. Since the ethics of minor sibling donation of BM have been well accepted, the following discussion will focus on the additive risk/benefit of treating the donor with G-CSF – which is needed either for G-BM or G-PB as the donor source.

Benefits to BMT recipients based on the donor source

A. Benefits to a G-CSF product in adult recipients

Initially, allogeneic cells for BMT were harvested directly from the BM; this method currently represents about 50% of all allogeneic BMTs in adults as reported by the IBMTR. Over the past several years there has been a transition in adult SCT to utilize G-mobilized PBSC (G-PB) over BM because of the lower early post transplant morbidity and mortality. This transition was based on four large randomized trials (1-4) that demonstrated the safety and efficacy of using G-PB for allografting. Inherent to the use of G-PB as the donor source is that the healthy donor is pretreated with G-CSF for 4-5 days prior to apheresis during which the hematopoietic progenitors are collected. This is identical to the proposed study, and provides most of the data on safety of short-term G-CSF treatment in normal adult and child donors. Two of the G-PB studies demonstrated a benefit in either overall survival (3) or disease-free survival (1) for recipients of G-PB as compared to unstimulated BM cells, but randomized studies and registry data (5) also reported more chronic GVHD in the recipients of the G-PB cells. Current data as to how chronic GVHD affects survival or quality of life (QOL) after G-PB transplants is limited and it is not known whether long-term adverse effects of chronic GVHD may eventually offset the early benefits of G-PB transplants. Nevertheless, the present standard of care is to use PBSC obtained after G-CSF stimulation as the cell source for related donor allogeneic transplantation of adult patients.

Table 1 summarizes the experience with G-BM and G-PB, focusing primarily on G-BM. Three Phase II studies (6-8) have demonstrated the safety and feasibility of using G-BM for allografting are similar to unstimulated BM. The rationale for exploring this approach is that there is potentially great benefit to the recipient with more rapid hematologic recovery, at the same time lowering the GVHD risk as a result of the lower T cell content of BM products. A secondary possible benefit could be a decrease in the volume of marrow harvested – which could decrease the morbidity of marrow donation, at least in a small part. In a small randomized Phase 3 comparison of G-PB and G-BM in matched sibling transplants, Morton et al (9) reported comparable hematological recovery with substantially lower overall chronic GVHD (47% vs. 90%; $p < 0.02$) and a strikingly lower extensive chronic GVHD (22% vs. 80%; $p < 0.002$) in recipients of G-BM. This trial suggests that the assumptions are valid and requires repeat in a larger clinical trial(s). All trials with G-BM or G-PB have shown feasibility and no unexpected donor complications.

B. Benefits in pediatric recipients

G-CSF stimulated BM presents a number of potential benefits to transplant recipients. Although G-PB provides more rapid post BMT hematopoietic recovery resulting in shorter hospitalization, its use results in a higher rate of chronic GVHD, resulting a poorer long-term outcome and quality of life. By contrast, G-BM appears to provide the benefit of shorter post BMT recovery while not incurring the greater chronic GVHD risk (16). In fact, one paper suggest that the rate of chronic GVHD may be lower than that post BMT with unstimulated BM (17) and that the TRM was decreased as well. In addition, the use of G-BM taken in identical volumes as unstimulated BM should result in decreased TRM and graft failure associated with high nucleated cell doses (46).

Conclusions: G-PB has emerged as the standard for adult allogeneic BMT. There are clear survival benefits in adult studies to G-PB as compared to unstimulated BM, at the cost of an increased rate of chronic GVHD. The extent to which this translates to pediatric patients is unclear. G-BM has the potential to provide the benefits of G-PB to pediatric patients (i.e. higher cell dose) without the major risk (chronic GVHD). This question can only be addressed in a phase III randomized study. A successful study will be a major advance in pediatric transplantation.

Donor risks

A. Risks to the adult donor of unstimulated BM versus G-BM and G-PB

For donors, hard outcomes such as complication rate and risk of mortality with the stem cell collection procedure need to be determined. The two strategies (PB or BM harvesting) differ quite markedly in terms of what is required from the donor, however, and there may be associated differences in donor QOL (e.g. anticipatory anxiety, symptoms, and duration of time lost from work, etc.). To date, few studies have addressed these issues in the related donor. Some studies have reported donor QOL, but none has compared donation of G-PB vs. G-BM. Published studies of unrelated donors (who provide anonymous stem cells for purely altruistic reasons) report less discomfort than do studies of related donors. (18) Certain techniques, such as use of long-acting local anesthetics after marrow donation, may decrease the pain further. (19) Growth factor use in normal donors is commonly associated with a need for pain relief, particularly for severe back pain. There are rare reports of major complications (e.g., splenic rupture) when G-CSF is given. Two studies of the first 493 unrelated donors who participated in the National Marrow Donor Program suggest that the risk of acute complications is low (6%), and that most donors experience positive psychological benefits from marrow donation.

A review of 8296 donors reported to the IBMTR between 1980-1989 revealed 24 life threatening or incapacitating complications for an incidence of 0.29% (20, 21). The NMDP recently reviewed serious events in 9345 normal donors (21). Serious events were noted in 125 cases (1.34%). Most events were mechanical (59%; nerve, bone, or tissue injury), with another large group of events associated with anesthesia. In this cohort, 40 patients (0.4%) had disabilities described as moderate to severe symptoms that took a prolonged period of time prior to recovery. Between 9 and 11 deaths have been reported worldwide for an estimated incidence of 1 death per 10,000 donations (20).

B. Risks to the pediatric donor of unstimulated BM versus G-BM and G-PB

Exactly how these estimates of common and rare side effects of marrow donation translate to the pediatric population is unclear. In 128 children (22) less than age 10 and an additional 343 donors from ages 10 to 19, life-threatening complications in donors under age 20, similar to adults, were rare (2/507, 0.39%). Another Seattle paper described harvests from 23 donors under age 2 (23). Most of these patients required allogeneic PRBC transfusion after their harvests due to the large volume of marrow required for older, larger recipients. Donors as small as 3.95kg have been reported (24), and a survey of pediatric transplanters showed that nearly 90% of centers were willing to harvest children less than 6 months old (25).

While several studies have shown some benefit in adult recipients receiving either G-CSF primed marrow or stem cells, large trials demonstrating clear benefit of these interventions in pediatric recipients have not been performed. In spite of this, use of G-CSF in pediatric donors prior to stem cell harvest is becoming more common. Data from the Pediatric Blood and Marrow Consortium, representing approximately 75 transplant centers in the PBSC with 26% of the matched sibling allogeneic procedures performed in 2002. Several other pediatric centers are administering G-CSF to donors prior to marrow harvest as part of a Pediatric Blood and Marrow Consortium (PBMTc) G-BM pilot.

Published experience regarding acute effects of G-CSF in normal children is primarily limited to PBSC collection. Donor complications in 61 pediatric donors harvested by the Spanish cooperative group (26) demonstrated significantly fewer side effects compared to an adult cohort (41% vs. 71%). The level of the toxicity and whether the effects were due to G-CSF or the apheresis procedure was not outlined, but of all patients (adult and pediatric) experiencing "toxicity," bone pain occurred in 90.5%, headache 21.5%, nausea 3%, and fever 1.5%. Kawano describes side effects in 19 pediatric PBSC donors in more detail suggesting an age-related difference in pain symptoms secondary to G-CSF. Of their 19 donors, 0/9 children under age 10 experienced discomfort with G-CSF administration, while 5/10 children >age 10 complained of mild headache or fatigue (treated only with acetaminophen) (27). The PBSCT Study group of Japan published a study expanding the Kawano experience which briefly described side effects of 57 donors between the age of 9 months and 24 years in age. Bone pain was described in 17.5% and headache in 5.3% during G-CSF therapy (relieved by non-steroidal medications). Forty donors had follow-up complete blood counts at a median of 25 months and no abnormalities were noted (28).

Two PBMTc trials have been developed to lay the groundwork for the proposed G-BM study. These data directly address some of the issues raised in terms of availability of pediatric data. The SCT0212 study retrospectively reviewed 218 PBSC or DLI collections in 201 pediatric donors ranging from 8 months to 17 years in age, with 56% of the collections on children 12 and under and 17% on children under age 7. With an average G-CSF dose of 10 mcg/kg/d for a mean of 4.4 days, less than 20% of children required pain medication, with a trend toward less pain with younger donors. No pain was reported in children under 7 and pain that did occur required at most acetaminophen, except for 1 teenage patient who required an oral narcotic (0.5%) (29). The PBMTc SCT0233 pilot study of G-BM is currently underway to provide further safety information in pediatrics. The study gives normal pediatric donors G-CSF at a dose of 5 µg/kg/d for five days prior to marrow harvest, piloting the approach we have proposed, and records daily age-appropriate pain assessments and use of analgesics. This 40 patient study is almost complete, and preliminary data show that in the first 32 patients minimal pain was reported, with no patient requiring narcotic pain relief (30). No other significant events or unusual side effects have occurred in either of these studies.

C. Rare serious events associated with G-CSF therapy

Because most event reporting after G-CSF therapy occurs in patients with underlying cancer or marrow failure disorders, defining the exact incidence of rare, serious events in normal donors is difficult. Major categories where an increase in rare serious events is possible include allergic reactions, flares of underlying autoimmune disorders, vascular events, and splenic rupture. Data from the German Donor Registry gives insight into these complications (36). Of 5930 normal donors reviewed (BM=2,644; PBSC 3286) and a total of 21,332 observation years, rates of these complications were compared between those who received G-CSF (PBSC donors) and those who did not (BM). Seven patients noted a flare of arthritis (5), hypothyroidism (1), or sarcoidosis (1) in the PBSC group compared to 2 patients who flared with sarcoidosis (1) and multiple sclerosis (1) after marrow donation. Whether there is an increase in vascular events after G-CSF treatment is equally difficult to judge. The German group reported three strokes and one myocardial infarction occurring at 0.25 to 2.5 years after G-CSF primed donation as opposed to one patient who developed Brown-Sequard syndrome after marrow donation. The challenge in judging whether autoimmune or vascular events are increased after G-CSF therapy is that there are a large number of older PBSC donors now entering the pool

to participate in reduced intensity conditioning regimens, and these older donors may have a higher incidence of these complications as a baseline.

Splenic enlargement was noted at baseline in 18% of severe congenital neutropenia (SCN) patients and 12% of cyclic or idiopathic neutropenia patients who subsequently received extended therapy with G-CSF. G-CSF leads to an increase in palpable splenomegaly to 38% in SCN patients, with a much smaller increase for the other categories of neutropenia (31). No splenic ruptures were noted in children receiving G-CSF therapy for neutropenia, even after years of therapy. Spleen size was studied in 84 healthy PBSC donors receiving G-CSF at a dose of 7.5 µg/kg/day for 5 days. Average change noted was an increase of 11mm in length (a 10% increase in volume) (37-39). A second study showed that spleen size increased in 95% of donors with a mean length increase of 13%. The spleen size returned to baseline by 10 days after the therapy was given (38, 39). Approximately 5 cases of splenic rupture have been reported in adult donors of PBPC (40-43). The incidence is estimated to be between 1:5000 to 1:10,000 (21). Again, splenic rupture has not been reported in children.

Conclusions: Operative BM donation has a low but defined risk of major complications, including death. Short-term G-CSF administration for G-PB or G-BM harvest is mainly complicated by discomfort, less pronounced than the harvest procedure itself, and less common in children than in adults. Thousands of normal donors and hundreds of children have received G-CSF for this purpose. The risk of significant complications of G-CSF administration is small compared to the already low risk of operative marrow harvest.

Lack of association of G-CSF therapy with malignancy

Theoretical concerns exist about short-term growth factor therapy potentially increasing the long-term risk of leukemia and thus increasing the risk of blood or marrow donation for normal donors. Extensive experience with growth factor therapy in pediatric patients with other diseases, combined with long-term follow up data from adult PBSC donors gives insight into this risk. Extended G-CSF therapy in patients with congenital neutropenia (Kostmann syndrome) has been associated with progression to MDS or AML in 12% of patients at 8 years. There is a clear consensus that this is due to the underlying disorder, as these patients are at significantly increased risk for progression to leukemia without cytokine therapy. In contrast, no patients treated with cyclic or idiopathic neutropenia in the Severe Chronic Neutropenia International Registry have been reported with progression to cancer, even with thousands of patient years of cytokine therapy (n=305, average length of cytokine therapy, 4.7 years) (31). Similarly, no long-term adverse hematologic effects have been noted in a two year follow up of neonates treated with G-CSF for sepsis (32).

Studies in normal adult PBSC donors have shown no late effects associated with short-term G-CSF therapy with 3-6 years of follow up (33,34). A review of 101 donors of Seattle PBSC trials who received a median dose of 16 µg/kg/d of G-CSF for a median of 6 days has had no leukemia association reported. Registry data from North America and Europe can offer further insight into the theoretical risk of progression to leukemia after G-CSF therapy in normal donors. The NMDP recently reviewed 9345 marrow collections and found that 6 donors had developed cancer. Reviewing donors who had received G-CSF for PBSC donation, the NMDP noted 4 cancers in 2370 donors, but none of the tumors were hematological malignancies (renal cell, breast, lung and cervical) (21). An extensive survey of EBMT data on normal donors harvested between 1990 and 2003 was conducted. Of 28,134 marrow donors assessed, 9 developed a hematological malignancy after donation for an incidence of 0.032%. Those receiving G-CSF for collection of PBSC had an equivalent incidence of hematological cancers (5/16,431 or 0.030%) (35).

The challenge of detecting increased risk when serious events are rare

Incidence data of serious events after the use of G-CSF presented above show that major events are very rare. A key event that is vital to track is that of hematological malignancy development after G-CSF use. Because

the incidence of leukemia in the pediatric and adolescent normal population is very low to begin with (about 35 to 50 per 1,000,000/ year) and because the latency period for development of leukemia can be from 3-8 years after exposure to a causative agent, in order to detect a 10 fold increase in leukemia, it has been estimated that a minimum of 2000 normal donors would need to be followed for 10 years. An additional factor is the fact that siblings of patients with cancer have an increased risk of leukemia and other cancers. Thus, to the extent that any theoretical rare effect of G-CSF can be detected, it could only be detected in the setting of a randomized study.

Overall conclusions. Tens of thousands of normal bone marrow and stem cell donors and patients without a malignancy have received G-CSF. Use of G-CSF in donors is standard of care in adult BMT and widely used, without study, in pediatric BMT. Use of G-CSF adds minimally to the toxicities and negligibly to the serious risks of operative BM donation. All of these toxicities and risks are probably less likely in pediatric donors than adult donors. There is currently no evidence to suggest that there is an increased risk of malignancy associated with a single short course or longer courses of G-CSF therapy.

The ethical framework in which we perform BM harvest in normal children is based entirely on the benefit to the donor, which comes from an increased likelihood of her sibling's survival. A study which has the potential to improve survival in BMT recipients is completely consistent with the ethical treatment of pediatric patients and their sibling donors.

Table 1. Summary of previous clinical studies

Author (Ref #)	Recipient Age (y)	Time to Engraftment, ANC (days)			Chronic GVHD (%) A: All cases; E: Extensive			Relapse (%)			Overall Survival (%)			
		BM	GBM	GPB	BM	GBM	GPB	BM	GBM	GPB	BM	GBM	GPB	
GPB														
Watanabe ⁽⁴⁷⁾	0.5-19 related donor			13			A 64% E 47%						10% TRM 38% high risk 78% std risk OS	
GBM														
Couban ⁽⁶⁾	17-61	22	18 ^S				A 45E 9%						41% OS 21% TRM	
GPB vs BM														
Couban ⁽³⁾	19-64 AML	23		19 [#]	A 69% E 30%		A 85% E 40%						16% TRM 60% 3yOS	7% TRM 68% 3yOS ^S
Ringden ⁽⁴⁸⁾	16-65 AML	19		14 [#]	A 32%		A 46% [#]	61% LFS CR1			57% LFS CR1	23% TRM 65% OS CR1	24% TRM 65% OS CR1	
Ringden ⁽⁴⁸⁾	16-62 ALL	19		14 [#]	A 40%		A 49% [#]	30% LFS CR2			34% LFS CR2	29% TRM 34% OS CR2	25% TRM 45% OS CR2	
Eapen ⁽⁴⁹⁾	8-20	18		13 [#]	E 21%		E 37% [#]	49% 4yRFS			42% 4yRFS	13% 18mTRM 47% 4yOS	27% 18mTRM 52% 4yOS	
GPB vs GBM														
Morton ⁽⁹⁾	16-60		16	14			E 22% E 80% ^S						67% OS	64% OS
Serody ⁽⁵⁰⁾	13-55		16	17			A 37% A 68% ^S						81% d100 54% 2yOS	100% d100 60% 2yOS
GBM vs BM														
Ji ⁽¹⁷⁾	12-41 CML	21	15 [#]		A 33%		A 24%	67% DFS 11% REL	78% DFS 13% REL			22% TRM	9% TRM	
Isola ⁽¹⁶⁾	15-59	24	17 ^S					48% EFS 13% REL	58% EFS 15% REL			25% TRM	24% TRM	

ALL: acute lymphocytic leukemia; AML: acute myeloid leukemia; ANC: absolute neutrophil count; BM: bone marrow; CML: chronic myeloid leukemia; CRx: complete remission x-year; DFS: disease-free survival; EFS: event-free survival; GBM: G-CSF-stimulated bone marrow; GPB: G-CSF-stimulated peripheral blood; LFS: leukemia-free survival; xyOS: x-year overall survival; REL: relapse; RFS: relapse-free survival; TRM: transplant-related mortality; \$: p<0.05; #: p<0.01

Appendix References

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