Safety of AlloPBPCT donors: Biometrical considerations on monitoring long term risks

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Summary: Up to now there are no data on long-term effects of allogeneic peripheral blood cell transplantation (AlloPBPCT). In particular, long term effects on healthy donors by the mobilization procedure which includes the exposition to G-CSF over several days are unknown. Recently the possibility of an increase in risk for acute leukaemia in this cohort has been discussed. Systematic long-term safety monitoring for AlloPBPCT donors cannot be adequately planned without agreeing on a both relevant and reasonably pessimistic hypothetical size of the increased leukaemia risk to be detected if present. Using data on leukaemia after treatment for Hodgkin's disease as example it is argued that a) excess leukaemia cases should be expected to occur predominantly between 2 and 10 years after the leukaemogenic event and b) a reasonably pessimistic guess would expect about 0.5% leukaemia cases at 10 years in AlloPBPCT donors. Such a tenfold increase over the general population's 10 year leukaemia incidence would be relevant, but require long-term follow up of several thousands of donors to demonstrate or exclude. In conclusion, safety monitoring for AlloPBPCT donors can only be organized on an international scale.

Introduction: Allogeneic peripheral blood cell transplantation (Schmitz 1995) may replace AlloBMT as procedure of choice in the near future. Many studies are under way to demonstrate the feasiblility and short term safety of the new procedure - both for the donor and the patient. Short term toxicity for the donor seems to be acceptable (e.g. Bensinger et al 1993). But long-term results are not yet available. Donor safety considerations are particularly of concern when unrelated donors are involved.

Objective: Given the current lack of data, discussing potential long-term risks of peripheral blood progenitor cell harvest using G-CSF mobilization for the donor is purely speculative. Up to now there is no indication that there are relevant long-term risks at all. Nevertheless the present paper will try to derive a guess at the size of a hypothetical risk for the donor in a reasonably pessimistic scenario. Such a consideration is no prediction, but only intended for use in the statistical design of adequate monitoring of donor safety.

This paper will focus on the potential size of a hypothetical risk to induce or promote leukaemia in the donor by the exposition to G-CSF during mobilization. There may be other sources of concern, which deserve separate consideration. No attempt will be made in the discussion to distinguish between commercially available G-CSF variants which theoretically may differ in side effects.

Background: The unease (Donadieu 1993) with the exposure of healthy donors to G-CSF is related to the fact that acute leukaemia cells carry receptors of various growth factors including G-CSF (e.g. Kondo 1991) which can be used for stimulation in vitro and which seem to play a role via an autocrine loop in autonomous growth of leukaemia cells (Russel 1992). Thus G-CSF might stimulate or promote preleukaemic cells present in the donor.

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In patients with haematological disorders, such as myelodysplastic syndrome, aplastic anaemia and congenital neutropenia, acute leukaemias have been reported after administration of G-CSF (Donadieu 1993, Izumi 1994, Wong 1994, Imashuku 1995). But in these diseases acute leukaemia can also develop in the course of the disease without any external G-CSF. Thus a systematic risk assessment is difficult. Furthermore, in these cases G-CSF had been typically administered for a considerable time.

It has been argued that the leukaemogenic potential of therapeutic G-CSF levels can be expected to be negligible, since elevated endogenous G-CSF levels can be observed during bacterial infections. Can one exclude an increased leukaemia risk a priori?

Endogenous G-CSF levels in healthy persons are in the range of 20-90pg/ml (Gabrilove 1993). During bacterial infections endogenous levels in the range of 800pg/ml up to 4000pg/ml are reported (Omori 1992, Pauksen 1994). Therapeutic peak concentrations are dose dependent in the range 20,000 to 400,000pg/ml, half life was calculated as 163 minutes (Vincent 1994) and therapeutic G-CSF levels may stay above 10,000pg/ml for 10-16h (Gabrilove 1993). Thus, therapeutic levels are about 2 to 4 log above normal endogenous and about 0.5 to 2 log above naturally elevated levels observed during bacterial infections. In addition, to our knowledge there has been no systematic long-term follow up for leukaemia after severe bacterial infections; so less than dramatic effects may have been missed. Therefore a hypothetical increased leukaemia risk cannot be excluded apriori, although the natural existence of high endogenous G-CSF levels supports a low risk hypothesis.

Biometrical discussion: What increase in leukaemia risk could be reasonably assumed in a pessimistic scenario? To derive a crude upper bound, experience from the treatment of Hodgkin's disease may be helpful. In the data of N=12411 patients from the International database on Hodgkin's disease (IDHD) (Henry-Amar 1989) the 10 year cumulative leukaemia rate was 2.2%. Treatment was stage related and consisted of radiotherapy and/or chemotherapy. In advanced stages MOPP polychemotherapy with well known dose dependent leukaemogenic potential was used in most cases. The rate of 2.2% includes the effect of salvage therapy. Up to 10 years after treatment 143 leukaemia cases were observed. 4.36 cases would have been expected based on published incidence data. Thus the observed over expected ratio was about 33.

In a model of leukaemia induction fitted to the IDHD data, therapy induced excess leukaemia cases typically occured between 2 and 10 years after the leukaemogenic event (Loeffler to appear). This indicates the time scale on which to expect excess leukaemia cases.

It seems safe to assume that mobilization of peripheral blood progenitor cells by G-CSF is considerably less leukaemogenic than standard chemotherapy and/or radiotherapy regimens used in the treatment for Hodgkin's disease.

The annual incidence of akute leukaemia in the US is reported to be 5 / 100 000 per year; this roughly translates in a cumulative incidence of 0.05% at 10 years. Thus 0.5% leukaemia cases at 10 years might be a reasonably pessimistic guess. This assumes that G-CSF mobilization carries about 1/4 the risk of treatment for Hodgkin's disease or - equivalently - increases the natural risk by a factor of 10.

A tenfold increase in leukaemia risk for healthy AlloPBPCT donors would be clinically relevant. But even in this magnitude it is fairly difficult to demonstrate or exclude it statistically. In order to observe 9 excess leukaemia cases in the assumed pessimistic scenario more than 2000 donors would have to be followed up over 10 years. Thus single center experience will almost certainly provide only anecdotal evidence.

Crude population based incidence data would not be sufficient as controls. Since donors are

HLA-matched to patients and related donors share even more genes with the patients, there might be a somewhat increased leukaemia risk among donors as compared to an unrelated and unmatched group. Thus a control group of BMT-donors of equal size is necessary to safeguard against false alarm triggering far reaching consequences.

Such a donor safety monitoring can only be done in a carefully planned study on an international scale. It will not be easy to conduct and finance. To make it feasible at all, there should be an incentive for donors, perhaps in form of an additional insurance which depends on compliance with regular follow up.

Conclusion: The first unrelated AlloPBPCTs have already been performed. If long-term AlloPBPCT donor safety is to be monitored, an international cooperation has to be organized without delay.

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