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Failure to effectively treat chronic graft-*versus*-host disease: a strong call for prevention

We read with great interest the paper by Palmer and colleagues (*Haematologica 2015;100:690*)[1] entitled "Failure free survival in a prospective cohort of patients with chronic GvHD". The study "highlights the poor outcomes in patients with cGvHD and the unsatisfactory ability of currently available therapies to control the disease adequately". Though we agree with these conclusions, we could go one step further: if chronic GvHD is so frequent, especially with the widespread use of peripheral blood (PB) grafts, and if we have strong evidence that we are currently unable to treat it, we should put more effort into prevention. How can we prevent cGvHD? There are two options. Either we go back to bone marrow (BM) as a stem cell source, which is known to reduce cGvHD as compared to PB, or we use PB, with some form of *in vivo* or *ex vivo* T-cell depletion (TCD).

Several arguments are raised against the use of BM, firstly that it increases relapse, based on the meta-analysis published in 2009:[2] in that meta-analysis, PB graft recipients had an 8.8% reduction of relapse, but 50% of the patients had chronic myeloid leukemia (CML). A recent randomized study,[3] published in 2012, showed no difference in relapse between PB and BM grafts from unrelated donors (UD), and only 10% had CML. Today we are not transplanting CML, certainly not in the chronic phase, so the argument that a PB graft prevents relapse is based on old data, in a patient population with a large proportion of CML. A second argument against BM , is that BM harvest is more hazardous for the donor than mobilization and stem cell collection, but this is also questionable.[4] The third argument is that many centers have not performed a BM harvest for years, and are therefore unable and/or unwilling to proceed with a BM harvest: this argument is probably the weakest, and should not enter in a medical decision.

The second option is to use PB, but add *in vivo* T-cell depletion:[4] prospective randomized trials in 668 patients, have shown that anti-thymocyte globulin (ATG) given in the conditioning regimen prevents chronic GvHD.[5-8] The first two studies were performed in the UD setting, with two different ATG preparations in BM transplants[5] or mostly in PB transplants (>80%).[6] They have come to almost exactly the same conclusion, although published 10 years apart: the reduction of extensive chronic GvHD in ATG patients, from 41% to 15% in the first study and from 43% to 12% in the second study.[5,6] Overall survival was unchanged in the two studies. The third ATG study was performed in the HLA identical setting for AML patients receiving a myeloablative PB transplant, with a calcineurin inhibitor and methotrexate for GvHD prophylaxis, with or without ATG.[7] Overall survival was unchanged, and extensive cGvHD was reduced from 52% to 8% in the ATG patients (P=0.005); cGvHD and relapse-free survival at 2 years improved with ATG from 17% to 37% (P=0.005).[7] The fourth study was performed in patients with UD grafts and has shown a reduction of moderate/severe cGvHD from 29% to 13% in patients receiving either a myeloablative or reduced intensity conditioning (RIC): at 1 year 37% of patients given ATG were free of immunosuppressive therapy, compared to 17% for patients not receiving ATG.[8] Thus, the addition of ATG reduces cGvHD, improves the proportion of patients off immunosuppressive therapy, and significantly increases the chance of surviving free of cGvHD and relapse.

Alternative ways to prevent GvHD, such as the use of alemtuzumab, post-transplant high-dose cyclophosphamide (PT-CY), or selective *ex vivo* T-cell depletion have all shown to be effective in single arm studies, but need to be tested in prospective trials.

It should be said that 3 of the 4 ATG randomized studies were performed in patients given a myeloablative conditioning, and one also included 30% of patients given a RIC regimen. Although a retrospective study in RIC transplants has shown an increased risk of relapse for patients receiving either ATG or alemtuzumab,[9] the most recent Canadian randomized study shows that also for RIC transplants, cGvHD can be reduced without increasing the risk of recurrence of the original disease.[8]

Indeed, although chronic GvHD has a protective effect on leukemia relapse,[10] one could ask how much is required to protect patients without increasing NRM. We have looked at our own database for the effect of cGvHD

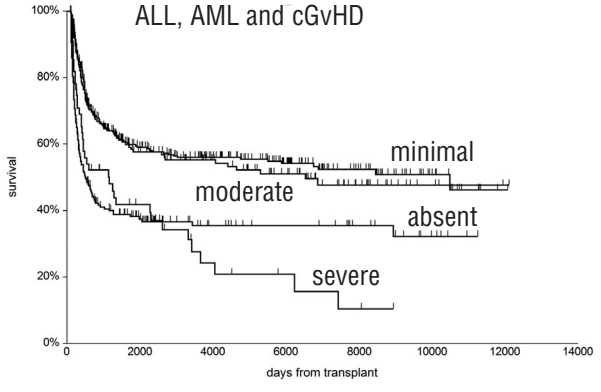

Figure 1 The effect of chronic GvHD on survival in patients with acute leukemia (n=819), alive on day +100 post-transplant. The actuarial survival at 20 years is as follows: absent cGvHD (n=224; 35%), minimal cGvHD (n=377; 52%), moderate cGvHD (n=163; 47%), severe cGvHD (n=55; 15%).

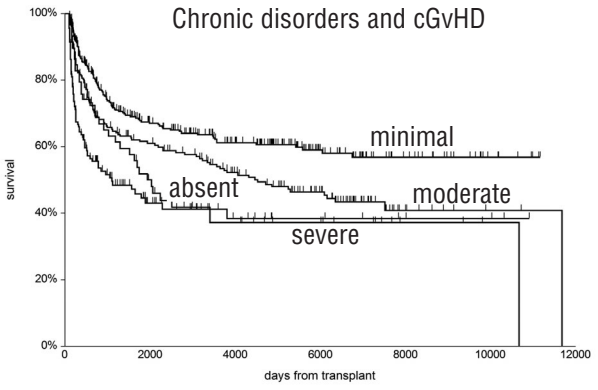

Figure 2. The effect of chronic GvHD on survival in patients with chronic disorders (n=914). alive on day +100 post-transplant. The actuarial survival at 20 years is as follows: absent cGvHD (n=176, 35%), minimal cGvHD (n=416; 56%), moderate cGvHD (n=248; 42%), severe cGvHD (n=74; 31%).

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on long-term survival at 20 years: Figure 1 depicts the effect of cGvHD on acute leukemias (n=819) (314 acute lymphoblastic and 505 acute myeloid leukemias) , and Figure 2 depicts the effect on chronic disorders (n=914) including chronic myeloid leukemias (n=374), myelodysplastic syndromes (n=186), lymphomas (n=156), myelofibrosis (n=93) and myelomas/lymphoproliferative disorders (n=105). Minimal cGvHD provides the best survival advantage over no cGvHD; moderate cGvHD shows equal or worse survival when compared to minimal cGvHD; severe cGvHD is always significantly worse than minimal cGvHD. Therefore we need to protect our patients from moderate and, especially, severe cGvHD, and all four randomized ATG studies have been able to reduce by 3-fold severe/extensive cGvHD, with no detrimental effect on survival.

Because of the increasing use of PB grafts following myeloablative conditioning regimens, and because of the negative effect of cGvHD on morbidity and mortality, it is our responsibility to advise transplant centers that PB grafts given without some form of T-cell depletion, especially after a myeloablative regimen, whether from UDs or matched siblings, should be discouraged, like smoking, because it is hazardous for the patients health: centers may consider using BM and/or *in vivo* TCD.

In conclusion, Palmer and colleagues[1] have convincingly shown that we have little to offer our patients with cGvHD , thus raising the issue of "prevention": today we know this is possible, to a large extent, using BM or PB with *in vivo* T-cell depletion, without jeopardizing survival.

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