

as determined by molecular technology, have significant predictive value for transplant related morbidity and mortality (TMM) and thus transplant outcome. Thus, a computer search often identifies only potential serological matches with further molecular typing needed to determine whether the serologic "6 of 6" match is a molecular "10 of 10 match" or less. The requisition, transportation and molecular typing procedure of donor samples are time consuming (2-4 weeks). Added to the 2-4 weeks of clearing, scheduling and preparing the donor for hematopoietic stem cell harvest, the median time from start of the formal search to infusion of the unrelated stem cells currently is 50-60 days in the U.S., only able to be further shortened if and when more donors are listed in the MUD registries with their complete molecular class I and II typing, and or if able to use one or more unrelated umbilical cord bloods (UCB) as the stem cell source. In the U.S., efforts are being made in collaboration with European UCB programs to not only generate large UCB banks, but to assure that the UCB stored is of maximum cellularity and quality. The potential of receiving appropriate hematopoietic stem cells in the form of UCB within 2 weeks of a request, has resulted in a significant rise of UCB transplants in adults in the U.S., with preliminary results being encouraging, but with the number of adult patients treated, combined with a short follow-up, making it difficult to declare this as a "standard of care" hematopoietic stem cell source for adult patients today, for which reasons most of such transplants are (and should be) done on investigational protocols.

The discrepancy in risk of TMM and mortality between patients with MyMal undergoing an alloSCT using an unrelated or related stem cell source was significant in disfavor of MUD alloSCT up to 10 years ago, but has greatly decreased in the last 10 years, especially if comparing 10/10 matched unrelated stem cell sources to HLA-identical sibling stem cell sources, regardless of the age of the patients. For older patients undergoing NST or RIC transplants, some data even suggests that MUD derived alloSCT's carry a benefit over family matched, mainly in reducing the risk of post-transplant relapse of the original MyMal, but also with no, or only minimal increase in the risk of TMM. However more data and longer follow-up is needed before any firm conclusions can be made as to the relative merits or current differences of using MUD derived hematopoietic stem cells vs. matched related stem cells.

Conclusion

Improvements in identifying patients with MyMal who most likely will benefit from an alloSCT and those who most likely will not, combined with the ability to administrate a graft-versus MDS/AML effect in the (older) group of patients with the highest incidence of these diseases, has set the stage for a more appropriate use of alloSCT in patients with these diseases, perhaps even laying the ground for a consensus as to what patients with MyMal should be transplanted and what patients should not, a consensus that currently does not exist.

Improvement in molecularly matching unrelated donors to patients, and the development of more safely using UCB transplants in adults, may result in more patients with MyMal in need of an alloSCT undergoing this procedure, a development strongly needed as in 2006, approximately 80% of patients dependent on identifying an unrelated donor source were unable to proceed to an alloSCT in the U.S.

Today, only a select, heterogeneous group of patients with MyMal is undergoing alloSCT of any type, including from MUD's. This in combination with improvements rendered from using new potent medications in patients with especially MDS, makes for an ongoing controversy as to which patients with MyMal should proceed to an alloSCT. However, further improvements in the diagnosis, risk allocation and non-transplant treatment of patients with these diseases may diminish this controversy.

E07 Stem cell transplantation in ALL: a donor versus no donor comparison in the EORTC ALL-4 study

B. Labar, S. Suciu, P. Muus, R. Willemze, J.P. Marie, G. Fillet, Z. Berneman, B. Jakšić, W. Feremans, D. Bron, H. Sinnige, M. Mistrik, G. Vreugdenhil, R. De Bock, D. Nemet, C. Gilotay, S. Amadori, T. de Witte, for the EORTC Leukemia Group. *Dept. of Medicine, University Hospital Center and School of Medicine, Zagreb, Croatia*

Allogeneic stem cell transplantation (allo-SCT) has been routinely performed as postremission therapy for ALL. But still compared to standard maintenance chemotherapy or autologous stem cell transplantation the role of allo-SCT is unclear. In high risk ALL patients allo-SCT has the advantage compared to other treatment options [1], but for standard risk patients this was not proved [2]. In the EORTC ALL-4 trial the postremission treatment outcome was analyzed according to donor versus no donor comparison.

Patients and Methods

In the ALL-4 trial for induction therapy patients were randomized either to receive prednisolone or dexamethasone together with standard chemotherapy. Patients younger than 50 years of age with a family donor who achieved CR with induction therapy and/or consolidation were assigned to undergo allo-SCT whereas patients without the donor were planned to be autografted or treated with chemotherapy.

Results

A total of 325 patients entered the trial. The median age was 32 years (range 15-72), M/F 187/138. ALL/NHL 313/12, B-ALL/T-ALL 217/90, mediastinal mass 11,4%, WBC $<30 \times 10^9/L$ 67%, CNS involvement 21%. Among 212 patients < 50 yrs, 189 (85.2%) reached CR; 198 patients were HLA typed; 90 had a donor and 108 had no sibling donor. The

Table 1. Patients < 50 yrs in CR1 assigned to be allografted according sibling donor availability

EFS/Survival status (%) at 5 years	Outcome of patients < 50 years who achieved CR1 (%)					
	All patients		Prednisolone group		Dexamethasone group	
	No donor	Donor	No donor	Donor	No donor	Donor
CCR	36	39	34	43	39	36
Relapse	58	38	63	35	57	40
TRM	5	23	3	21	4	26
DFS	36	41	33	46	37	38
Overall survival	38	42	37	55	38	39

five-year DFS was similar for patients with or without donor (41% for donor group vs. 36% for no donor group, $p=0.38$, Table 1). The relapse incidence was significantly lower (38% vs. 58% $p<0.05$, Table 1), and TRM was significantly higher (22% vs. 3%, $p <0.05$, Table 1) for patients with a donor. Patients with a donor randomized to receive prednisone in induction therapy showed a trend for a lower TRM and similar antileukemic efficacy compared to dexamethasone group

(Table 1). The patients with a donor received prednisone in induction therapy have the advantage of survival compared to patients without the donor (55% vs.39% at 5 years, Fig. 1). The better survival was also observed for the patients with a donor receiving prednisone compared to patients with a donor receiving dexamethasone (55% vs. 39% at 5 years, Fig. 2).

Conclusions

Analysis by intention to treat of the EORTC ALL-4 trial reveals that the policy to perform an allo-SCT in case of sibling donor is available does not result in a significantly better outcome than to offer auto-SCT or maintenance therapy. The lower relapse incidence in patients with a donor was annulled by a higher TRM. Patients with a donor receiving prednisolone for induction therapy have the advantage in survival. This data speaks in favor that less intensive immunosuppressive regimen before transplant might decrease transplant toxicity and thus with the similar antileukemic efficacy might improve the treatment outcome.

References

- [1] Thiebaut A; Vernant JP; Degos L et al. Hematol Oncol Clin North 2000; 24:1353-66
- [2] Larson R.A. www.UpToDate®, online, 2007.

E08 New tyrosine kinase inhibitors in chronic myeloid leukemia (CML)

H. Kantarjian, J. Cortes. Department of Leukemia, University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA

Introduction

Imatinib therapy produces complete cytogenetic responses in 70% to 85% of patients with CML in early chronic phase. With a median follow up of 5 years, the annual rate of resistance/progression is 4% and of mortality 1-2% [1]. The estimated 5-year survival rate is about 90% [1,2]. Resistance to imatinib, in 30% to 50% of resistant cases, is through point mutations of the BCR-ABL kinase domain. Over 40 different mutations have been reported which can produce absolute (e.g. T315I), relative, or no resistance to tyrosine kinase inhibitors (TKIs) [2]. The degree of resistance depends on the mutation location and its selective effect to specific TKIs [3-6]. Other mechanisms of resistance include BCR-ABL-dependent (e.g., overexpression and amplification) and BCR-ABL- independent mechanisms (e.g., overexpression of Src-related kinases) [4]. New-generation TKIs, or non-TKI agents may overcome or prevent the development of resistance. These are discussed below.

Dasatinib (Spryse; BMS-354825)

Dasatinib is an ATP-competitive, dual-specific Src- and Abl-kinase inhibitor. Src activation may play a role in the

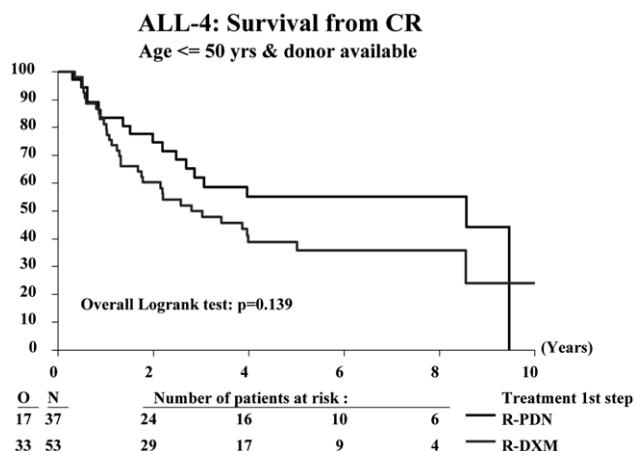


Figure 1. Survival from CR for patients with a donor randomized to receive prednisone (R-PDN) or dexamethasone (R-DXM)

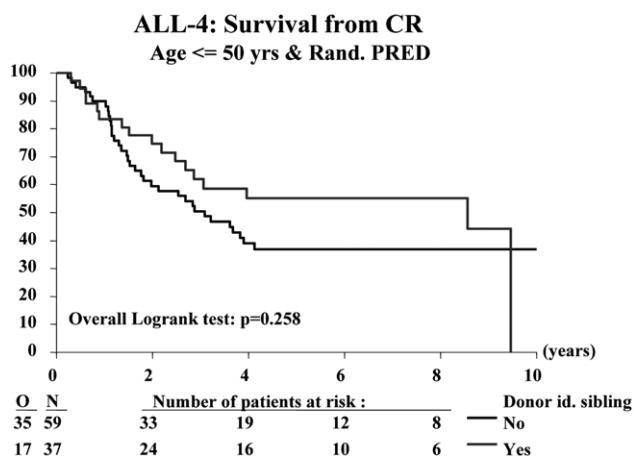


Figure 2. Survival from CR for patients receiving prednisone according to donor availability