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Allogeneic hematopoietic stem cell transplantation after immunosuppressive but non-myeloablative conditioning: "miniallografts" are no small matter

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Conditioning regimens for allogeneic hematopoietic stem cell transplantation (SCT) usually involve high-dose chemoradiotherapy given in doses that are *myeloablative* or at least severely myelotoxic. Such conditioning has been considered essential for several reasons: a) to clear the marrow of host hematopoietic cells, b) to make space for the infused stem cells, c) to be sufficiently immunosuppressive to avoid rejection of the donor cells by the recipient's residual immunologically-competent cells;[1] d) the conditioning was also deemed essential for eliminating or at least drastically reducing the patient's neoplastic cells in transplants for malignancy. Since recurrence of the tumor after SCT continues to be an important cause of treatment failure, attempts have been made to improve disease-free survival by increasing the intensity of the conditioning regimen. Unfortunately, this approach has led to a parallel increase in early transplant-related mortality and usually no benefit in overall survival.[2]

Over the past years it has become increasingly evident that alloreactivity of donor immune cells against the host's tumor plays a major role in controlling or eradicating the patient's malignancy after allogeneic SCT. This phenomenon (ie, the graft-versus-leukemia or graft-versus-tumor (GVT) effect) was first clinically identified[3] and has been recently confirmed by the results of donor leukocyte infusions (DLI) in chronic myelogenous leukemia (CML) and other hematologic malignancies which relapsed after an allogeneic SCT.[4,5] The possibility of eradicating high tumor cell burdens by adoptive allogeneic cell therapy through DLI in patients failing intensive conditioning regimens suggests that an important component of the curative potential of SCT may be achieved through the induction of a state of host-versus-graft tolerance plus the effect of donor-derived T-lymphocytes that recognize and eradicate host-derived tumor cells and most normal stem cells. For this purpose myeloablative conditioning may not be essential. In fact, the induction of host-versus-graft tolerance is usually accomplished by successful stable donor cell engraftment, without the need for immunosuppression.

With this background, investigators from the MD Anderson in Houston[6] and the Hadassah University Hospital in Jerusalem[7] have pioneered a new concept in the area of allogeneic SCT. Some investigators have termed this approach *miniallografts* to highlight the low-intensity of the conditioning regimens used. In summary, these authors have used conditioning regimens including purine analogs, mostly fludarabine, since they are potent T-cell immunosuppressive agents with little myelotoxicity, in conjunction with less than high doses of cytotoxic drugs. As the source of hematopoietic stem cells, both teams have used G-CSF-mobilized peripheral blood stem cells due to their higher content of progenitor cells and greater engraftment potential with respect to bone marrow.[8] For patients with myeloid malignancies the Houston team has reported the combination of fludarabine plus standard-dose cytosine arabinoside and idarubicin,[6] and for chronic lymphocytic leukemia or myeloma fludarabine has been combined with cyclophosphamide or melphalan, respectively.[9] An important aspect of the Houston experience is that these *miniallografts* have been used for patients who were deemed uneligible for a standard allogeneic SCT, basically because of their advanced age, the median being around 60 years. Slavin *et al.*, on the other hand, have included all patients eligible for an allogeneic SCT, with a median age of only 31 years, in a protocol that combines fludarabine with busulphan (8 mg/kg) and antithymocyte globulin. As expected, early transplant-related toxicity has been very low, similar to that of conventional chemotherapy. More important is that donor cell engraftment has been the rule in all patients who have not suffered leukemic relapse. Early results of chimerism studies performed by sensitive PCR-based methods have shown that

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mixed chimerism is common during the first weeks. Later on, it is frequent that recipient-derived cells slowly disappear and complete donor chimerism develops. This may suggest that once a state of tolerance is achieved, the engrafted donor-derived immune and hematopoietic cells progressively replace both normal and malignant cells. This host-versus-graft tolerance may, however, not be accompanied by graft-versus-host tolerance. In fact, Slavin *et al.* observed grades II-IV acute graft-versus-host disease (GVHD) in 10/26 patients, and Giralt *et al.* reported 3/15 such cases, with later development of chronic GVHD in 9 patients of the former study. In the Jerusalem report 22 of 26 patients were alive and 21 were disease-free after a median follow-up of 8 months. These preliminary studies, together with other anecdotal reports,[10-12] appear very encouraging.

In the current issue of Haematologica, Carella *et al.* report an interesting study on this subject.[13] Although only nine patients were included, their experience is noteworthy for various reasons. First of all, these authors have designed a protocol combining maximal tumor cytoreduction achievable by conventional conditioning and an autologous SCT with subsequent allogeneic SCT after an immunosuppressive but minimally myelotoxic preparative regimen. The latter included fludarabine plus conventional-dose cyclophosphamide, as previously reported by Khouri *et al.*[9] Conceptually, this tandem approach could avoid the toxicity of upfront conventional allogeneic SCT and optimize the potential GVT effect in a setting of minimal residual disease after autologous SCT. In fact, adoptive immunotherapy after allogeneic SCT by DLI appears to be more effective against minimal residual disease, and the alloimmune GVT effect requires several weeks to months to take effect.[4] By reducing the total tumor load and/or decreasing tumor growth the donor's immune system may be given a better chance to mount an effective GVT response.

Secondly, two of the patients reported had post-transplant courses that shed some light on the mechanisms that may lead to long-term disease-free survival following these *minialloграfts*: one patient with CML in the second chronic phase and another with refractory anemia with excess of blasts and a t(1;3) translocation. Following fludarabine plus cyclophosphamide only mild cytopenias occurred, but detailed study of the donor-recipient chimerism patterns by PCR and cytogenetics revealed that hematopoiesis slowly reverted from 100% recipient before SCT to around 50% on days +75 and +20 post-transplant, respectively. More interestingly, this was accompanied by a decrease in malignant cells with complete disappearance of bcr-abl transcripts on day +122 and of the translocation t(1;3) on day +53, respectively. Donor-derived cells, on the other hand, progressively increased reaching 100% in bone marrow and peripheral blood on days +108 and +63, respectively. Among the other seven patients, peripheral blood chimerism studies also showed a progressive increase in donor-derived hematopoiesis, reaching complete donor chimerism on days +60 to +210 in four cases, while one patient transplanted for CML in blast crisis showed autologous reconstitution. Three of these patients with Hodgkin's disease (n=2) and low-grade non-Hodgkin's lymphoma are said to have been only in partial remission after the autologous SCT but achieved complete remission after the allogeneic SCT. However, the short interval between both procedures (39 days in one case and 40 days in the other two) and the short follow-up after the allogeneic SCT (2, 4 and 6 months) makes it very difficult to demonstrate that a true partial remission after the first transplant reverted to a complete remission after the *miniallograft* in such a short time interval solely due to a GVT effect.

Taken together, these studies demonstrate that donor derived cells can effectively engraft following non-myeloablative conditioning, with progressive replacement of recipient cells through a GVH reaction. Whether or not fludarabine is an essential component for these *minialloграfts* and what preparative regimens are optimal for different indications will require further studies. Additionally, since relapse continues to be an important cause of treatment failure after conventional allogeneic SCT, it seems unlikely that a single *miniallograft* will lead to long-term disease-free survival for most patients, and later intervention with DLI may be appropriate in this setting.[7] GVHD, both acute and chronic, will probably still be a problem in these patients, and post-transplant prophylaxis should be used until more clinical experience delineates the incidence, patterns and outcome of GVHD after *minialloграfts*. However, the excellent short-term outcome of most patients in the published studies makes *minialloграfts* a fascinating new area of clinical investigation, particularly suited for elderly patients or those with medical conditions that contraindicate an otherwise potentially curative allogeneic SCT.

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