

## Allogeneic Cell Therapy: The Treatment of Choice for All Hematologic Malignancies Relapsing Post BMT

To the Editor:

I read the article of Hans J. Kolb on behalf of the European Group for Blood and Marrow Transplantation working party with great interest.<sup>1</sup> This article attempts to summarize the present state of the art in treating relapsed leukemia following allogeneic bone marrow transplantation (BMT) with donor lymphocyte infusion. Ignoring previously published observations have lead the authors to a number of wrong conclusions, which must be reconsidered in view of existing data.

First, the authors refer in their introduction to the first patient treated with transfusion of donor lymphocytes, quoting their own reference.<sup>2</sup> Dr Kolb and some of his colleagues should have been aware of earlier quotations of both the concept and the first patients treated with donor lymphocyte infusions as reported in several abstracts in Blood,<sup>3-6</sup> meeting reports,<sup>7</sup> papers in referred journals<sup>8-10</sup> and a review.<sup>11</sup> The issue is not ignoring the original observations and successful pilot clinical trials published earlier, quoting selectively one's own, which is not infrequent among colleagues and scientists. What is even worse is the fact that the report talks clinicians away from attempting to try adoptive allogeneic cell therapy (allo-CT) in patients with acute lymphoblastic leukemia (ALL) who have relapsed following allogeneic BMT, although patients with ALL relapsing following allogeneic BMT were previously successfully treated with allo-CT. In fact, the first patient ever treated successfully with allo-CT, as early as November 1986, was a patient with ALL and he was the one who paved the road for using allo-CT late post BMT as a potent therapeutic modality for the treatment<sup>3-6</sup> or even prevention<sup>12</sup> of relapse in patients failing allogeneic BMT. This patient was a 2½-year-old boy with a very aggressive form of pre-B cell ALL transplanted in second resistant relapse. Allo-CT was considered as soon as he relapsed again 1 month following BMT, this time with bulky extra-myeloid disease accompanying overt hematological relapse, both of which responded extremely well to repeated infusions of his sister's peripheral blood lymphocytes (PBL). This patient is currently alive and well and disease-free, with negative polymerase chain reaction for male DNA, >8 years following BMT. Details of this patient were previously presented in Dr Kolb's report at the last meeting of the International European Bone Marrow Transplantation Society. Moreover, since then successful reversal of relapse was accomplished by our team in a total of 4 out of 6 patients with ALL, in 3 only following the addition of recombinant human interleukin-2 (rIL-2) concomitantly with infusion of donor PBL.<sup>13,14</sup>

It seems important to bring these data to the attention of Blood because in view of the conclusions of Kolb's paper<sup>1</sup> many hematologists may not wish to attempt treating patients with ALL relapsing following allogeneic BMT, a complication that is unfortunately not infrequent. Because no effective alternative treatment is available for patients relapsing post BMT, patients with ALL, like patients with any other hematological malignancy, should be offered the therapeutic benefits of allo-CT as soon as relapse can be diagnosed, contrary to the conclusions of Kolb's report, preferably at the stage of minimal disease. Alternatively, considering the amount of tumor cells at the time relapse is diagnosed and the rate of tumor cell growth, before debulking by chemotherapy should be considered to permit sufficient time for the development of graft versus leukemia effects.

Overall, the cumulative international experience indicates that allo-CT should be considered as the treatment of choice for treating relapse in both acute and chronic leukemia. As it appears that all tumor cells derived from hematopoietic stem cells may be susceptible to allo-CT, donor PBL infusion should be considered for the

treatment of all hematological malignancies, including EBV-induced posttransplant lymphoma and most likely, although the data is not yet sufficient, for treatment of other lymphomas as well. Moreover, patients with resistant disease may still respond to allogeneic donor T lymphocytes further activated in vivo by rIL-2.<sup>4,10,11,13</sup>

In view of the growing clinical experience, the previously described information should serve as a reminder not to give up hope and intensive therapeutic efforts when a patient relapses early or late following allogeneic BMT, because posttransplant immunotherapy may reinduce durable remission. Considering unmaintained disease-free survival extending beyond 5 years with elimination of all detectable evidence of disease or host-specific markers by sensitive molecular methods, one might dare to define the long-term remission inducible by allo-CT as complete cure.

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## Response

The letters of S. Slavin and J. Mehta raise the issue about the first treatment of recurrent leukemia with the transfusion of donor lymphocytes. Our original report on the treatment of recurrent chronic myelogenous leukemia after bone marrow transplantation with transfusion of donor lymphocytes was published in *Blood* 1990.<sup>1</sup> In a more recent report in *BLOOD* we summarized the experience of the European Cooperative Group of Blood and Marrow Transplantation (EBMT) was evaluated and our earlier report cited.<sup>2</sup> Regretably neither Slavin nor Mehta<sup>3</sup> have contributed their patients to the EBMT analysis. A single patient of S. Slavin was not included because this patient was selected from a larger group of patients and treated in a different way.

We were aware of the important contributions of the Hadassah group in the field of graft-versus-leukemia (GVL). We have not cited their work, because we considered their approach as basically different from ours. Slavin's approaches included transfusion of lymphocytes from HLA-mismatched donors and the use of stimulatory cytokines in patients treated with autologous transplantation,<sup>4</sup> and the repletion of T cells in graded doses early after transplantation of T-cell depleted marrow from HLA-matched donors.<sup>5</sup> Repletion of T cells has not significantly improved the probability of remission, but increased significantly the incidence of acute graft versus host disease (GVHD).<sup>6</sup> Obviously repletion of T cells even in small increments cannot circumvent the therapeutic dilemma of T-cell depletion for prevention of GVHD. The GVL effect is ablated with the depletion of T cells.<sup>7</sup> Our approach was completely different and based on observations in animal experiments. Transfusion of donor lymphocytes could not abrogate tolerance in stable rat<sup>8</sup> and dog<sup>9</sup> chimeras. Own experiments in dogs with T-cell depleted DLA-matched marrow grafts have shown that GVHD is invariably induced by transfusion of donor lymphocytes within 2 months of transplantation, but the transfusion of donor lymphocytes failed to induce GVHD more than 2 months after transplantation, ie, after transplantation tolerance was established.<sup>10</sup> Even large numbers of lymphocytes did not induce GVHD. Nevertheless chimerism could be improved and immunity transferred from the donor to the host. An antileukemia effect in the absence of GVHD was observed after delayed infusion of donor cells in mice.<sup>11</sup> In human patients best results were obtained in patients with chronic myelogenous leukemia.<sup>2</sup> Some patients with acute myelogenous leukemia and myelodysplastic syndrome have responded to the transfusion of donor lymphocytes. No success has been reported in this analysis in acute lymphoblastic leukemia treated by donor lymphocyte transfusion without any other therapy. However, there may be exceptions. The patient of Slavin was treated by

graded doses of T cells very early after transplantation, and an infant reported by Ferster et al<sup>12</sup> responded to the transfusion of cells from his HLA-haploidentical father. We did not intend to discourage attempts of treating acute lymphoblastic leukemia with donor lymphocytes, but on the basis of the results reported a combination of the transfusion of lymphocytes with either chemotherapy or cytokines should be recommended.

Unlike experimental animals about 48% of human patients did develop GVHD of grade 2 or higher.<sup>2</sup> Escalating the dose of T cells<sup>13</sup> and depletion of CD8<sup>+</sup> T cells from the transfusion<sup>14</sup> may be ways to circumvent severe GVHD without losing the GVL effect. There are many ways of adoptive immunotherapy, but chimerism and stable transplantation tolerance are preconditions.

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