EDITORIAL

Graft-Versus-Leukemia: No Longer an Epiphenomenon

By Joseph H. Antin

". . . if . . . the dose of X-rays were insufficient to kill 100 per cent of the leukaemic cells . . . homologous marrow might . . . be able to produce an immune reaction to destroy any surviving leukaemic cells . . ." (Barnes and Loutit, 1957[1])

THE PRINCIPLE that the transplant conditioning regimen might be inadequate to completely eradicate leukemic hematopoiesis and that the antileukemic effect of infused marrow elements contributes to the ability of marrow transplantation to cure leukemia was first proposed by Barnes et al in 1956.[2] Although their studies and the studies of subsequent investigators in murine models generally confirmed the existence of a graft-versus-leukemia (GVL) effect,[3] data in humans were entirely indirect. Mathé et al[4,5] rationalized early efforts at marrow transplantation by invoking a GVL reaction, but evidence for this phenomenon was first provided by Weiden and the Seattle transplant team.[6,7] They showed that the likelihood of relapse was substantially lower in patients with either acute or chronic graft-versus-host disease (GVHD) compared with unaffected patients. A higher relapse rate after syngeneic transplantation compared with allogeneic transplantation was shown retrospectively[8] and confirmed with a larger retrospective study performed by the International Bone Marrow Transplant Registry.[9] Furthermore, a GVL effect was inferred when recurrent leukemia after marrow grafting regressed after a GVHD flare associated with the discontinuation of immunosuppression.[10-12] Finally, extensive experience with ex vivo T-cell depletion of the marrow showed a strong association between T-cell depletion and relapse, especially in chronic myelogenous leukemia (CML).[9,13-16] On the other hand, Sullivan et al[17] attempted to harness the GVL effect by either reducing the intensity of GVHD prophylaxis or infusing buffy coat cells immediately after the transplant, but they were unable to manipulate GVL to a clinical advantage. There was no reduction in relapse rate, and there was substantial mortality due to transplant-related toxicity and GVHD.[17]

The first direct evidence of a GVL effect in humans was provided by Kolb et al[18] when they used a combination of interferon-α and buffy coat cells obtained by leukapheresis to induce cytogenetic remissions in three patients whose CML had relapsed after allogeneic marrow transplantation. Excitement over these observations led to rapid confirmation by several independent groups of investigators, including a report by Drobyski et al[19] in this issue of *Blood* (Table 1).[19-24] Although details of the protocols differed, these investigators have shown that allogeneic buffy coat mononuclear cells have a striking capacity to identify and destroy CML in vivo, resulting in a composite clinical response rate of 83%. The potency of the GVL response is very impressive. Detection of the *bcr-abl* mRNA transcript with reverse transcriptase polymerase chain reaction (PCR) using nested primers has a sensitivity of 1 Philadelphia chromosome-bearing cell per 10^6 normal cells.[25] There are approximately 10^{12} leukemic cells in the blood and marrow during clinical relapse. Once leukemic cytoreduction and reestablishment of normal hematopoiesis occur, any residual leukemic cells are diluted into 10^{12} normal cells. Thus, to achieve a remission documented by PCR the number of leukemic cells in the body must decline 1 million-fold to less than 10^6, because a 1 million-fold cytoreduction approaches the limit of detectability of *bcr-abl* against the background of normal cells. Even fewer leukemic cells may survive the GVL reaction; several patients have been observed for more than 2 years without relapse and without detection of *bcr-abl* transcripts. Undoubtedly the leukemic stem cells that are eliminated by GVL are present at a much lower frequency in the marrow. Nevertheless, the antileukemic effect is very potent, and a retrospective comparison of the disease-free survival reported in these studies with second marrow transplantation shows that both the relapse rate and therapy-related mortality are substantially lower with buffy coat infusions.[26,27]

Interestingly, it appears that the GVL reaction is more effective in chronic-phase CML than in other hematologic malignancies or advanced CML. For example, Sullivan et al[17] may not have observed a GVL effect in their early trial, in part, because there were no patients in the trial with chronic-phase CML. Retrospective analyses support the presence of a GVL effect in non-Hodgkin's lymphoma[28,29] and the acute leukemias,[9,21] but further studies will be needed to determine whether it can be induced reliably with buffy coat or T-cell infusions. The ability to treat relapsed CML without the morbidity and mortality of a second transplant is unquestionably a valuable contribution to the care of these patients. However, these promising studies raise a number of interesting questions.

WHAT IS THE ROLE OF INTERFERON-α?

A proportion of patients with chronic-phase CML respond to interferon-α therapy with a reduction in the frequency of cells containing the Philadelphia chromosome, although PCR can still detect *bcr-abl* gene rearrangements. Similarly, interferon-α treatment of patients that relapsed after marrow transplantation has proven clinically useful, but it does not eradicate residual disease or prevent relapse.[30] Clearly, interferon-α has pleomorphic physiologic effects. Not only does interferon-α mediate an antiprolifera-

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Table 1. Summary of Published Data Using GVL for CML

	n	IFN	Mononuclear Cell Dose ($\times 10^8$/kg)	Clinical Response	*bcr-abl*(−) by PCR	Cytopenia	Acute GVHD*	Therapy-Related Death
Kolb et al[18]	3	3/3	4.4, 5.1, 7.4	3/3	ND	0/3	2/3	0
Jiang et al[20]	2	0/2	1.8, 2.7	2/2	2/2	0/2	1/2	0
Bär et al[22]	6	3/6	0.34-5.2	5/6	4/5	2/6	5/6	1
Drobyski et al[19]	8	6/8	2.5-5.0	7/8	5/6	4/8	7/8	1
Helg et al[23]	3	3/3	3.8, 5.7, 12.3	3/3	2/2	3/3	3/3	1
Porter et al[24]	8	8/8	0.9-7.9	7/8	5/8	7/8	7/8	1
Novotny et al[51]	6	6/6	NR	5/6	2/2	6/6	5/6	3
Frassoni et al[52]	10†	4/7	2-3 infusions	NR	NR	3/10	7/10	3
Summary		33/43 (77%)	0.34-12.3	32/36 (83%)	20/25 (80%)	25/46 (54%)	37/46 (80%)	10/46 (22%)

Abbreviations: IFN, interferon-α; NR, not reported; ND, not done.

* Grade I-IV GVHD.

† Seven of ten were treated for CML.

tive effect on leukemic cells, but it enhances cell-mediated immunity and the expression of both histocompatibility molecules and accessory cell molecules (eg, LFA-3, CD58).[31-33] As shown in Table 1, most patients receiving buffy coat also received interferon-α before and/or during mononuclear cell infusions. Because some patients responded to buffy coat infusions without interferon-α therapy, it is very unlikely that interferon-α alone is responsible for the molecular genetic remissions. In contrast to patients receiving interferon-α alone,[30] none of the patients that achieved a molecular genetic remission with buffy coat infusions have relapsed, although further follow-up will be required to estimate the durability of the response. Although it is appealing to think that interferon-α may augment the GVL effect, the data are insufficient to estimate the extent of its contribution, and this is a fruitful area for future studies.

WHAT ARE THE QUANTITATIVE AND QUALITATIVE PROPERTIES OF THE EFFECTOR CELLS RESPONSIBLE FOR INDUCING REMISSION?

All of the studies infused buffy coat obtained by leukapheresis of the original marrow donor. Drobyski et al[19] performed immunophenotyping studies on the infused cells and showed that the infused cells reflected the expected proportion of T cells, natural killer (NK) cells, and monocytes in normal donor blood. Although Drobyski et al[19] attempted to administer a standard dose of T cells, as shown in Table 1, variable numbers of mononuclear cells were infused in the various studies. Complete molecular genetic remissions were obtained with as few as 0.34×10^8 cells/kg; some patients receiving far larger doses had no response. Although most studies did not quantify the number of T cells infused, once a critical threshold of effectors has been surpassed, it is likely that minor histocompatibility differences are more important than the number of T cells. It will be important to establish a threshold dose of effectors to administer a sufficient number of cells to establish a GVL response but as few as possible to limit the risk of severe chronic GVHD.

Although it is not possible to come to firm conclusions about the identity of the effector cell based on current data, $CD4^+$ cells may be good candidates. Some patients appear to have $CD4^+$ T cells that lyse leukemic cells in vitro while sparing nonleukemic cells from the same donor.[34] The only clinical transplant data that begin to address this issue are the results of marrow purging with anti-CD8 monoclonal antibodies by Champlin et al.[35] Although the residual $CD4^+$ T cells were capable of causing GVHD, the incidence of GVHD was lower than would be expected with pharmacologic prophylaxis, and the relapse rate was much lower than expected. If the relapse rate remains low with adequate follow-up, it would be worthwhile to determine whether immunotherapy with $CD4^+$ T cells alone would provide the GVL effect divorced from GVHD.

NK cells are another candidate effector cell. They have a well-known ability to lyse K562, a cell line derived from a patient with CML, suggesting that enhancing NK cell numbers or activity might be clinically useful. Several studies have measured high numbers of NK cells in the blood after marrow grafting.[36,37] These cells are often capable of lysing cryopreserved, recipient CML cells in vitro[20] as well as inhibiting leukemic progenitor colony growth without affecting normal colony-forming unit granulocyte-macrophage (CFU-GM).[38] Interleukin-2 (IL-2) administration has been shown to increase NK cell or LAK activity after marrow grafting,[39,40] and it can be administered after T-cell–depleted allogeneic transplantation without exacerbating GVHD. When these trials are mature they may help determine whether IL-2 enhances GVL, and they may provide additional evidence that the GVL effect is independent of GVHD.

CAN GVL AND GVHD BE SEPARATED?

It appears that GVHD and GVL may be mediated by overlapping but not identical subsets of cells. If these populations can be defined, they can be exploited in an immunotherapy regimen. As noted above, $CD4^+$ T cells may be able to mediate GVL without GVHD. T-cell–depleted marrow transplantation for the treatment of CML is associated with a higher relapse rate than transplantation performed using standard prophylaxis even when controlled for similar de-

grees of GVHD. This observation implies that GVHD per se may not be entirely responsible for the GVL effect, but rather a cell population critical to GVL might be removed by the T-cell–depletion procedure. On the other hand, patients with acute myelogenous leukemia (AML) receiving T-cell–depleted grafts had a lower relapse rate than patients receiving syngeneic grafts, suggesting that an allogeneic effect can occur in the absence of GVHD.[9] The same data set showed that, in general, more severe GVHD was associated with a greater GVL effect. Murine models of GVL support the concept that GVL and GVHD can be mediated by separate as well as identical cell populations, ie, that cells responding to nonspecific host alloantigens cause GVHD and can have an antileukemic effect, but that there also may be a leukemia-specific reaction that can give rise to GVL without GVHD.[3] These observations lead to the possibility that CML-specific T-cell clones could be developed to improve the specificity of the response.

The acute marrow transplant setting may result in the preferential proliferation and differentiation of allospecific cells over leukemia-specific cells, resulting in more GVHD than GVL and an underestimation of the benefits of GVL. T cells infused in the milieu of the marrow transplant are exposed to higher levels of cytokines, adhesion molecules, and major histocompatibility complex (MHC) antigens that may contribute to the tissue injury that is interpreted as GVHD. When T cells are infused into histocompatible patients who are not subject to the toxicity of radiation, chemotherapy, and infection, the induction of cytokines and tissue injury may be less severe.[41,42] Consequently, GVL may be more prominent, because GVHD is less severe. In this context, it is interesting to note that all of the patients shown in Table 1 received very large doses of T cells compared with marrow transplantation but without the benefit of GVHD prophylaxis. Nevertheless, grade I-IV GVHD occurred in 80% of the patients, and it was clinically significant (grade II-IV) in 51%. Mortality was directly attributed to GVHD in only one patient. In contrast, when buffy coat was administered along with methotrexate immediately after transplantation, the incidence of grade II-IV GVHD was 82%.[17] Although the difference in GVHD incidence may be partly because of selection bias, the contribution of regimen-related injury to the development of GVHD should not be minimized. In addition to the clinical benefits of this therapy, the GVHD observed after immunotherapy provides an opportunity to clarify our thinking about the pathophysiology of GVHD, because it can be studied in the absence of regimen-related toxicity.

WHAT IS THE TARGET OF THE GVL RESPONSE?

It is likely that minor histocompatibility antigens that differentiate donor and recipient serve as targets for both GVL and GVHD.[43,44] However, if GVL can occur independently of GVHD, there also must be leukemia-specific antigens that can be identified by donor effector cells. One candidate antigen might be the p210BCR-ABL fusion peptide. Preliminary work suggests that specific, class II-restricted, T-cell–mediated immune responses can be directed against the novel joining region of this chimeric protein.[45] Demonstration of the fusion peptide on the surface of leukemic cells or presentation of the peptide by antigen-presenting cells will be necessary to confirm the significance of this observation. These studies raise the interesting possibility that leukemia-specific clones can be generated for clinical use or that a tumor vaccine could be developed.

HOW DOES DONOR MARROW RECOVERY OCCUR?

There are two possible mechanisms to explain hematopoietic recovery after buffy coat infusion. In most cases, restriction fragment length polymorphism (RFLP) analysis showed residual donor lymphohematopoiesis, suggesting that the eradication of leukemic hematopoiesis permitted the recovery of suppressed donor hematopoiesis. Secondly, the hematopoietic stem cells and progenitors infused during immunotherapy may contribute to blood count recovery. In mice, stem cells apparently can engraft without freeing a hematopoietic niche,[46] and a similar phenomenon might contribute to recovery in some of the patients whose hematopoiesis converted to donor without a period of pancytopenia. Several of the surviving patients required marrow infusions for full hematopoietic recovery, indicating that the combination of residual stem cells and peripheral blood stem cells was inadequate to reestablish hematopoiesis. Both patients with and without residual donor cells failed to recover, and how patients requiring marrow infusion differ from patients who enter remission without a period of pancytopenia requires further study.

The myelosuppressive effects of this therapy can be severe, and all of the treatment-related deaths listed in Table 1 were because of sepsis in the setting of severe pancytopenia often complicated by GVHD. This is reminiscent of transfusion-associated GVHD, in which normal hematopoietic cells can serve as a target of GVHD. However, major histocompatibility differences usually give rise to transfusion-associated GVHD, and it is more likely that the pancytopenia observed in these trials was because of leukemia-specific antigens or minor histocompatibility differences.[47]

FUTURE DIRECTIONS

The recognition that immunotherapy can be used successfully to treat relapsed CML leads to novel marrow transplantation strategies. Recipients of T-cell–depleted transplants can be monitored carefully using PCR to detect persistent *bcr-abl* mRNA transcripts. Buffy coat infusions can then be used before clinical relapse to suppress leukemic hematopoiesis. Although there are well-documented instances in which the transcripts persisted for long periods after transplantation and then spontaneously disappeared, Roth et al[48] have shown that greater than 75% of patients with ≥ 2 positive assays will relapse. A variant on this theme is to perform T-cell depletion on donor marrows then administer buffy coat to all patients in a form of prophylactic or preemptive immunotherapy. In both cases, patients would benefit from the reduction in acute GVHD-related toxicity during the transplant, but still benefit from the GVL effect. Murine models show the feasibility of this approach.[49,50] As noted previously, it is likely that administra-

tion of T cells after the conditioning regimen-related toxicity has resolved will result in less risk of severe GVHD, although the risk of chronic GVHD is considerable. Such a strategy is currently under study by the Hadassah group.[50]

The use of allogeneic cells as adoptive immunotherapy is an exciting innovation in the therapy of relapsed CML, but its value in the treatment of other malignancies remains to be determined. Ultimately, the most useful outcome of these studies will be the insights into GVHD, cell-mediated immunity, hematopoiesis, and the biology of CML that we are likely to achieve.

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