EDITORIAL

Interleukin-2 in Therapy of Hematologic Malignancies

By Mario Szol and David R. Parkinson

The article by Gisselbrecht et al1 in this issue of Blood describes the activity of single-agent interleukin-2 (IL-2) in a heterogeneous group of previously treated patients with malignant non-Hodgkin’s lymphoma (NHL), Hodgkin’s disease, and cutaneous T-cell lymphoma (CTCL). The number of patients within each of the defined groups is relatively small, and the confidence intervals surrounding the observed response rates are correspondingly quite large. Nevertheless, the investigators are to be congratulated for accumulating this clinical experience and documenting the activity of single-agent IL-2 in these malignancies. Conducting phase II trials of a biologic agent in advanced lymphoma populations has proven exceedingly difficult, particularly when the agent, like IL-2, has substantial acute toxicity and requires inpatient administration. Several phase II trials of IL-2 alone or in combination with other agents were sponsored by the Cancer Therapy Evaluation Program of the National Cancer Institute (NCI) in both single institutions and major cooperative groups; with rare exception, most did not meet accrual goals and were closed prematurely. The reasons for this difficulty, although not entirely clear, are undoubtedly related to the relative sensitivity, even in relapsed patients and however transiently, of these neoplasms to chemotherapy. Furthermore, there is an understandable bias of investigators and practitioners to place these patients on second-line chemotherapy regimens or to proceed to high-dose chemotherapy with marrow transplantation, along with a reluctance to expose patients to agents that are unlikely to have a direct antitumor effect. These practices leave only a small population of patients that can meet the strict performance status and organ function eligibility criteria common to IL-2 protocols.

Reviews combining the results of several small studies of IL-2 alone or in combination with adoptively transferred lymphokine-activated killer (LAK) cells in patients with malignant lymphoma (including some patients reported in Gisselbrecht et al1) were recently published.2,3 Using this expanded database, one can conclude that IL-2 has low-level antitumor activity against follicular and diffuse NHL, and has some activity in Hodgkin’s disease. Activity has also been observed in patients with CTCL, but the numbers of patients treated have been too small to accurately determine a response rate. In general, the duration of most of the responses in all of these indications has been brief and the clinical significance marginal. However, a few patients (generally having a follicular histology) have had prolonged remissions lasting 12 or more months. In Gisselbrecht et al,1 two patients whose tumors were of T-cell origin and were limited to skin involvement and one patient with a B-cell diffuse large-cell lymphoma, also achieved prolonged responses.

These phase II data of IL-2 alone or with LAK cells in malignant lymphoma are of interest primarily for the biologic implications of the glimpse of activity observed in heavily pretreated patients. With the exception of CTCL, for which further phase II trials appear warranted, at this point it appears that single-agent IL-2 does not have sufficient activity to recommend its use routinely as a salvage therapy for relapsed lymphoma. However, the data raise several questions regarding further development of IL-2 in therapy for hematologic malignancies. These relate to the mechanism responsible for IL-2’s antitumor activity in these patients and whether the activity of IL-2 in patients with advanced disease could be enhanced by combination with other immunotherapy strategies or with chemotherapy. In addition, it raises the issue as to whether IL-2 might have greater activity if administered earlier in the course of the disease or in patients with minimal tumor burdens. Finally, there remains the question of an optimal dose and schedule of IL-2, and how the most appropriate regimens can best be determined through clinical investigation.

Unfortunately, very little is known regarding the mechanisms that mediate IL-2’s antitumor activity in hematologic malignancies. Despite years of careful clinical trials in malignant melanoma and renal cell carcinoma, diseases in which IL-2 has low but reproducible clinical activity, the numerous immunobiologic events leading to tumor regression remain unclear. The majority of preclinical data gathered in therapeutic models of IL-2 against several syngeneic animal tumors point to induction of an antigen-specific, major histocompatibility complex (MHC)-restricted T-cell response. In recent years, human melanoma antigens recognized by host cytotoxic T cells (CTL) have been identified and cloned; nevertheless, the correlation between induction (or presence) of a host CTL response against melanoma and response to IL-2 has not been conclusively proven. Lymphomas both of B- and T-cell type have long been recognized as potential targets of immunotherapy, because they are presumed to present tumor-specific antigens. Recently, evidence has been presented that a host T-cell response can be identified in vivo expanded tumor-infiltrating lymphocytes derived from a small percentage of lymphoma patients,4 and that a host T-cell proliferative response can be induced in some lymphoma patients by vaccination with host-derived idiomere.5 Although these data suggest that antigen-specific T cells may play some role in IL-2-generated responses, it is just as likely that IL-2’s antitumor activity against lymphoma and perhaps other hematologic malignancies may be produced by more varied and complex mechanisms related to the biology of IL-2 and of the malignant hematopoietic cells.
IL-2 can theoretically exert its effects by acting directly on the malignant cells, indirectly by inducing cytokines that themselves have a direct effect on the tumor cells, or indirectly by inducing antitumor effector cells. IL-2 therapy is associated with the induction of a cascade of secondary cytokines, including IL-6, interferon-γ, and tumor necrosis factor. In addition, lymphomas and hematologic malignancies in general express a wide variety of cytokine receptors on their surface, including, in some cases, functional receptors for IL-2 itself. The combined direct effects of IL-2 and induced cytokines on these malignant cells are difficult to predict. The situation is further complicated by the fact that other ligand-receptor interactions between the malignant cells and host immune cells induced or activated by IL-2, such as the CD40-CD40 ligand B-T cell interactions, may influence the ultimate fate of the malignant cell. Depending on the type of lymphoma and the cell surface receptors expressed, the cytokines induced by IL-2 and present in the local milieu, the activation state of the malignant cell, and the interactions of the lymphoma cell with other infiltrating immune cells, the administration of IL-2 could produce any one or a combination of the following outcomes in the malignant hematopoietic cell: apoptosis, protection from apoptosis, growth arrest, proliferation, differentiation, block of differentiation, or direct cytotoxicity.

The induction of activated natural killer (NK)/LAK cells as potential effectors either in vivo or in vitro for adoptive transfer has been an objective of many IL-2 trials. Although these cells clearly contribute to the antitumor effects of IL-2 in some animal models of both solid tumors and hematologic malignancies, their role in the antitumor activity of IL-2 in patients is unclear. In solid tumors, these cells are often not found in tumor biopsies of regressing lesions, and their number in peripheral blood before, during, or after treatment has not been found to correlate with response to IL-2 in patients with melanoma or renal cell carcinoma. Nevertheless, in vitro data show that many malignant hematopoietic cell types are very sensitive in vitro to LAK cytotoxicity. From animal model studies, it appears that the NK/LAK cell may have an important potential antitumor role in settings of minimal residual disease, such as purging of residual tumor in bone marrow or directly eliminating tumor in vivo after bone marrow transplantation. Furthermore, NK/LAK cells may enhance marrow engraftment by themselves producing colony-stimulating factors, and may suppress graft-versus-host disease (GVHD) after allogeneic marrow transplants.

Should clinical development of IL-2 for therapy of lymphomas proceed given the difficulty in predicting an outcome that itself depends on the unpredictable relative importance of all potential positive and negative regulatory influences by this cytokine on malignant hematopoietic cells? The answer appears to be a qualified yes, with some support from the example of the clinical experience obtained with another cytokine, interferon-α. The low level of activity of interferon-α as a single agent in NHL and evidence of synergistic activity with this cytokine in combination with chemotherapy in preclinical experiments were sufficient to justify its use in combination with chemotherapy “up front” and initiation of randomized trials to define the contribution of the biologic agent. Although the results have not been uniformly positive, several of these studies (particularly in indolent lymphoma) suggest a beneficial effect from the addition of interferon-α on disease-free survival. It is of interest that combinations of chemotherapy with IL-2 (plus or minus LAK or TIL) similarly have marked synergistic antitumor effects in animal models. In some of the models in which the mechanism of the synergy has been carefully studied, the antitumor effect of the combination is dependent both on the direct cytotoxic activity of the chemotherapeutic agent (perhaps through a major reduction in tumor burden) as well as on some inherent biologic activity of the IL-2 itself. Because melanoma and renal cell carcinoma, two solid tumors with some sensitivity to IL-2, are relatively resistant to chemotherapy, it has been difficult to test successfully in humans whether the preclinical results are predictive of IL-2/chemotherapy interactions in humans. The lymphomas may therefore represent one of the few human malignancies in which both chemotherapy and IL-2 are sufficiently active to warrant a clinical trial of the combination based on the animal model findings.

Several pilot trials have been initiated to determine the role of IL-2 alone or in combination with activated lymphocytes after high-dose chemotherapy and autologous marrow transplantation in patients with both lymphoma and leukemia. Investigators hope that IL-2 will induce a graft-versus-leukemia (GVL) effect at a time when patients have been optimally debulked to a state of minimal residual disease. The documentation that IL-2 has antitumor activity in both advanced lymphoma and leukemia patients has been considered to further support this approach, although it is not clear that the mechanisms relevant to response in the advanced disease setting would be operative in the post-marrow transplantation setting. A variety of animal models have documented the potential efficacy of this approach; however, the exact dose and timing of IL-2, the requirement for adoptive transfer of activated cells, and the actual cells responsible for antitumor activity (the GVL effect) appear to be somewhat model-dependent. Regardless of the exact mechanism, at least two groups have recently reported small pilot phase I trials showing the tolerability of the particular IL-2 regimen and the ability to activate NK cells in vivo in the posttransplantation setting. Furthermore, comparison of disease-free survival for acute myeloid leukemia (AML) patients posttransplantation in some of the trials appears to be superior to matched historical controls; this is in contrast to the poor results obtained in some of the studies for patients with acute lymphocytic leukemia (ALL). The value of IL-2 posttransplantation in patients with first relapse or second remission AML is now being evaluated in a prospective randomized study being conducted by the Southwest Oncology Group under NCI sponsorship. A similar study for patients with relapsed lymphoma has been proposed by University of Washington investigators (M. Benyunes and A. Fefer) and will be initiated soon under NCI sponsorship. Substantial interest has also been expressed for a study examining the ability of IL-2 to prolong survival when used as maintenance/consolidation after the induction of complete response in newly diagnosed AML patients.
An intriguing but unexpected potential application of IL-2 to lymphoma/leukemia treatment is the IL-2–induced suppression of GVHD in allogeneic transplants. Animal models have shown that use of IL-2 in combination with T-cell–depleted syngeneic marrow or donor/host NK cells early in the transplant period can prevent GVHD without altering the GVL effect.\textsuperscript{13} The exact immunologic mechanisms responsible for GVHD suppression are still unclear; nevertheless, a pilot clinical trial of IL-2 alone has been initiated in patients receiving allogeneic marrow transplants mismatched at 2 to 3 MHC alleles.

Another potential but still speculative area of investigation is the use of IL-2 in acquired immunodeficiency syndrome (AIDS)-related lymphomas. Preliminary data suggest that IL-2 may restore or improve some immunologic functions in a subgroup of these patients, including increases in CD4\textsuperscript+ T-lymphocyte counts, improvement in T-cell mitogenic responses, and enhancement of delayed hypersensitivity responses to recall antigens.\textsuperscript{14} The change in immunologic status may be sufficient to produce tumor regression, as noted for lymphomas developing in other immunosuppressed states. Such therapy would have to be administered in association with antiretroviral agents, given the known ability of IL-2 to induce retroviral expression in human immunodeficiency virus-infected cells. It is also possible that use of IL-2 to reverse immunosuppression may prevent the development or progression of lymphomas. The preliminary results of a phase II trial of IL-2 combined with zidovudine were recently reported.\textsuperscript{15} The regimen was tolerable and clinical antitumor responses were observed. Additional trials therefore appear warranted for this indication.

Although some therapeutic gains may be made by using IL-2 in the settings discussed above, it is an optimistic and perhaps unrealistic hope that substantial advances will be made with the nonspecific application of a single cytokine across a group of malignancies characterized by such biologic heterogeneity. When considering strictly immune-based approaches, IL-2 will probably be most useful when administered to support the induction, activation, and expansion of appropriate effector cell subsets, which must still be defined. We may be some time away from fully understanding the complex cascade of events that occur with IL-2 administration, and the interactions of those events with the complex biologic processes of the malignant cell. It can be hoped that carefully designed and conducted clinical trials may both further define the clinical benefits that can be achieved from the use of IL-2 in these malignancies, and yield clues to the relative importance of the various biologic mechanisms which may be involved in producing such benefit.

REFERENCES

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