Interleukin-2: Prospects for lymphocyte-mediated destruction of pediatric malignancies

Paul M. Sondel, MD, PhD
From the Departments of Pediatrics, Human Oncology, and Genetics, University of Wisconsin Clinical Cancer Center, Madison

Clinical observations of pediatric patients have provided important biologic observations of previously described “experiments of nature.” The study of inherited immune deficiency disorders has improved understanding of the immune system by enabling analysis of the separate cellular and humoral components and the variety of cell types involved in these immune responses. A critical factor in the control of these immune reactions is the lymphokine interleukin-2, a 15.5 kD molecular weight protein made by helper T cells, which acts in several ways on a variety of immune cells. Provision of IL-2 to some patients with immune deficiency disorders is producing evidence of clinical benefit. Similarly, physiologically “specific” immune suppression mediated by blockade of IL-2 action through IL-2 receptor inhibition is showing potential utility in the control of severe autoimmune disorders and allograft rejection.

A separate autologous “experiment of nature” has involved patients with leukemia receiving allogeneic bone marrow transplants. Documentation of a decreased chance of recurrence of leukemia after graft-versus-host reactions provided evidence of the existence of a graft-versus-leukemia effect. Multiple analyses of allogeneic BMT document that lymphocytes in the infused marrow are involved in this graft-versus-leukemia effect in patients with leukemia who are recipients of BMT.

To some extent all manipulations involving IL-2 as potential cancer treatment can be considered as clinical approaches attempting to simulate this graft-vs-tumor reaction identified initially in pediatric patients with leukemia. The purpose of this overview is to summarize the rationale and current prospects for manipulating these lymphocyte responses into effective antitumor therapy by means of IL-2.

Use of IL-2 in animal models. A variety of in vivo murine models show that administration of IL-2 at appropriate dosages and times can have striking antitumor effects. This has been documented with both immunogenic tumors and nonimmunogenic tumors. Responses to the immunogenic tumors appear more dependent on tumor-specific, antigen-reactive major histocompatibility complex-restricted T lymphocytes. In contrast, the action of IL-2 on nonimmunogenic tumors appears to be mediated primarily through activation of natural killer cells which, on exposure to IL-2, mediate the lymphokine-activated killer phenomenon, enabling them to destroy a vast array of tumor cell lines in vitro (and apparently in vivo). Clinical trials have been testing the clinical extrapolation of these animal data.

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<th>BMT</th>
<th>Bone marrow transplants</th>
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<td>IL</td>
<td>Interleukin</td>
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<td>LAK</td>
<td>Lymphokine-activated killer (cells)</td>
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<td>NK</td>
<td>Natural killer (cells)</td>
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Current clinical status of treatments with IL-2 for malignancy. The availability of human recombinant IL-2 enabled clinical studies to proceed with pharmacologic doses of this physiologic lymphokine. Because of the short half-life of IL-2, prolonged treatment with IL-2 (either multiple daily injections or continuous infusion) given for several days to weeks appeared necessary to induce significant immunologic activation in vivo. In an IL-2 dose-dependent manner, lymphocyte activation, lymphocytosis, and LAK activity can all be induced by in vivo administration of IL-2. In certain malignancies of adults, such as melanoma, renal cell carcinoma, and non-Hodgkin lymphomas, reproducible antitumor effects were seen with infusions of IL-2 alone or with infusions of IL-2 together with in vitro activated autologous LAK cell preparations. Although these responses
were seen in patients with refractory malignancies considered unresponsive to conventional treatment, only a minority (approximately 20%) had a measurable response. Furthermore, virtually all patients had significant dose-dependent, immune-mediated toxicities as a direct result of the induced immune activation by IL-2.

**Pediatric trials with IL-2.** Recently pediatric phase I and phase II trials involving IL-2 have been initiated. For example, the Children's Cancer Study Group (CCSG), in cooperation with the Pediatric Oncology Branch of the National Cancer Institute, has completed a phase I study of IL-2 showing that the maximum tolerated dose of IL-2 in children given continuous infusion is comparable to that obtained in adults treated with a similar regimen (Roper M, et al., manuscript in preparation). Other pediatric studies in North America and Europe are generating analogous results. Phase II studies testing the antitumor efficacy of IL-2 with single-agent therapy are now under way. Further improvements beyond those attainable with single-agent IL-2 treatment are essential, and preclinical data provide numerous leads.

**Prospects for combination therapies involving IL-2 for children with cancer.** Multiple animal models document enhanced immunologic antitumor efficacy if immune mechanisms are used early in the setting of minimal microscopic disease. Thus combining IL-2 with chemotherapy or radiation therapy has proved useful in murine models. Combining IL-2 with other recombinant biological agents such as interferon or tumor necrosis factor has also yielded synergistic results both in vitro and in murine models. Testing of these combinations is under way in adults and merits further investigation in children.

Presently it remains unclear whether most human malignancies are analogous to immunogenic or nonimmunogenic tumors; thus it remains uncertain whether to focus on the T cell or NK cell component of the IL-2 response. In either case there is a need to augment lymphocyte/tumor interactions to facilitate better antitumor responses. Several tumor-selective monoclonal antibodies have been generated for this purpose. Several murine monoclonal reagents reactive with a diganglioside (GD2) on neuroblastoma cells can facilitate binding of activated lymphocytes to tumor cells. Neuroblastoma target cells are dramatically destroyed in vitro by lymphocytes obtained from patients receiving IL-2, but this destruction is augmented several fold when tested in the presence of a murine anti-GD2 monoclonal antibody. Even more striking destruction is seen when a human mouse chimeric antibody against this same GD2 is used in the in vitro assay. A multiinstitutional CCSG clinical trial testing this concept directly in patients with refractory neuroblastoma by means of anti-GD2 reactive monoclonal antibody together with IL-2 is now under way. Murine data suggest using this combination in patients with minimal microscopic disease, possibly after autologous BMT. Further testing is required to initiate such combined clinical trials with IL-2 and monoclonal or chimeric antibody after BMT.

Allogeneic BMT currently has a definite role in the treatment of certain pediatric patients with high-risk leukemias. The identification of the graft-versus-leukemia effect suggests that a major component of the curative results from allogeneic BMT may be the immune mechanisms involved with the antileukemic T cells transferred with the bone marrow. If this is the case, a future goal for treatment protocols would be identification of the antileukemic immune mechanism to enable its incorporation into specific antileukemic therapy. Ideally such an immune-mediated approach might be specifically antileukemic and might not necessitate hematopoietic chimerism and the risks of graft-versus-host reactions associated with hematopoietic ablative and allogeneic transplantation. We recently developed an in vitro model to evaluate mechanisms that may be involved in the graft-versus-leukemia effect. Clonal selection of human T cells reactive with allogeneic leukemia has shown that rare T cells can mediate apparently specific destructive effects against allogeneic leukemia cells. Such T cells have been cloned and expanded, and show typical antigen-specific T cell reactivity with the use of αβ T cell receptor molecules able to recognize allogeneic leukemia cells but not remission lymphocytes from pediatric patients with acute lymphoblastic leukemia. If this phenomenon can be generalized, extrapolation of these in vitro results could lead to a therapeutic regimen. Studies in murine models indicate that in vivo transfer of large numbers of these cloned T cells combined with IL-2 may provide antileukemic reactivity that may be effective in the minimal disease setting. An appropriate clinical time to consider such therapy may be after engraftment with autologous BMT. Further preclinical work is required before considering clinical testing of such complex protocols with cloned T cells with tumor specificity.

**SUMMARY**

Immunologic therapy of cancer was speculated on at the turn of the century. In animals, in vitro, and most recently in patients, irrefutable evidence has been obtained that lymphocyte responses can have a reproducible and beneficial antitumor effect. These results indicate that "biologic response modification" may truly become a fourth modality for cancer treatment, to be integrated into the standard approaches of radiation, chemotherapy, and surgery. To what extent these immune approaches may enable eradication of microscopic amounts of residual diseases in children who would otherwise have a recurrence of their malignan-
cies remains the critical issue for testing over the next decade. Enthusiasm regarding this approach is abundant, but critical evaluation of all clinical trials is essential to best focus these mechanisms into effective therapy.


REFERENCES