EDITORIALS

Interleukin-2: Further Progress Through Greater Understanding

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Modifications of the original interleukin-2 (IL-2) regimen developed by Rosenberg and his colleagues (1) at the Surgery Branch, Division of Cancer Treatment, National Cancer Institute (NCI), have attempted to maintain or increase the antitumor effects of this treatment while reducing its toxicity. The article by Gaynor et al. (2) in this issue of the Journal represents another such attempt to improve upon the high-dose bolus regimen. This phase I study explored the dose of recombinant IL-2 that could be administered by continuous infusion together with lymphokine-activated killer (LAK) cells over a 5-day period.

Gaynor et al. obtained results consistent with those of other investigators. With continuous infusion of IL-2, they observed a range of toxic effects that were qualitatively similar to those observed by other investigators with bolus administration of IL-2. As with other high-dose IL-2 treatment strategies, the patients in this trial were treated to the limits of tolerance. Despite this fact, the dose-related increase in the incidence and severity of these toxic effects imposed an effective limit on the amount of IL-2 that could be delivered. Similar also to the results of other high-dose IL-2 trials was the observation of objective responses, including durable complete responses, in a minority of patients.

The study by Gaynor et al. appears at the same time as a large number of completed clinical studies involving IL-2 are entering the literature. Although the published trials conducted in this field have involved therapy with IL-2 administered in a wide variety of doses, schedules, and combinations with other agents, making comparative analysis difficult, it would appear that none of these manipulations have led to dramatic increases in response rates.

Nevertheless, there can be no doubt that IL-2 treatment can produce remarkable changes in the natural history of tumors in some patients with renal cell carcinoma and in some patients with melanoma. However, this group represents the minority of patients treated. Up to 5% of treated patients respond completely, and an additional 10%–15% respond partially, when response rates in different series are examined. These numbers are small enough that it has been difficult to demonstrate survival benefit overall for IL-2-treated patients as a group. These considerations, taken together with the significant toxicity of the high-dose IL-2 regimens, recently led the Biologicals Advisory Committee of the Food and Drug Administration to recommend against licensing approval at this time for single-agent IL-2 in the treatment of metastatic renal cell carcinoma. However, the compelling pre-clinical evidence that strongly suggests that this therapy can be significantly improved and the dramatic responses in individual patients make it appropriate to consider how best to further study the antitumor characteristics of IL-2-based therapy.

Despite this preclinical evidence, progress beyond the initial therapeutic steps with IL-2 has not been easy. The toxicity of the most intensively studied and reproducibly active IL-2 treatment schedule still limits the number of patients with renal cell carcinoma and of patients with malignant melanoma to whom it can be administered and has limited its study in other tumors. Although numerous other treatment schedules have been developed, and objective tumor responses have been demonstrated with many of these schedules, comparative phase III studies have not yet been performed to compare their efficacy with that of the original NCI Surgery Branch regimen.

Furthermore, the response rates may vary in the different tumors. While a randomized trial of bolus versus continuous-infusion IL-2 [using the regimen described by Gaynor et al. (2)] delivered to a similar level of toxicity and coadministered with LAK cells gave equivalent response rates in patients with renal cell carcinoma (3), the same continuous-infusion schedule of IL-2 appeared to be inactive in patients with melanoma (4). Similarly, the efficacy of ex vivo activated LAK cells administered with IL-2 may vary in different tumors. In studies from the Surgery Branch of the NCI, LAK cells did not add to the response rates observed with IL-2 alone in patients with melanoma, whereas they may have contributed to a higher objective response in patients with renal cell carcinoma (5). Randomized studies are in progress, in which the efficacy of high-dose IL-2 together with interferon α is being compared with that of IL-2 given alone. Despite the preclinical predictions, addition of other cytokines to IL-2 has not produced dramatic enough changes in response rate or quality to be declared clearly superior on the basis of phase II studies. Therefore, while dramatic improvements in the therapeutic efficacy of IL-2 with the addition of cytokines can be readily demonstrated in relatively small numbers of animals, phase II trials involving larger numbers of patients have not shown the same effects.

Despite the disappointing response rates observed with IL-2 therapy to date, an enormous amount has been learned in a relatively short time about the biologic basis of IL-2 therapy, including both the characteristics of its antitumor effect and its toxic effects. Some insight into the mechanism of response to IL-2 has been gained. The nature of the possible effector cells, for example, has been much more clearly defined, and the description of possible immunobiologic differences between renal cell carcinoma and malignant melanoma may explain some of the observed differences in response rates to different IL-2 schedules as well as suggest that, in the future, different therapeutic strategies for these tumors may be indicated (6). Recently, the pathophysiology of IL-2 toxicity has been much more clearly understood (7).
defined with respect to the cascade of cytokines generated with IL-2 administration, and new strategies are being explored to ameliorate these effects (e.g., the use of antibodies to tumor necrosis factor and the use of arginine analogue inhibitors of nitric oxide generation) (7,8).

A large number of biologic and clinical questions remain unanswered, however, and many clues exist as to how to proceed experimentally. While it is possible that the preclinical models are not predictive for the situation in patients, it is more likely that the immunobiologic heterogeneity of the patient populations under treatment, in contrast to the homogeneity of the preclinical models, defeats attempts to dissect the value of a single therapeutic manipulation in an individual trial. As a result, simple determination of response rates in the setting of limited numbers of biologically dissimilar patients in a phase II trial will not provide accurate tests of therapeutic hypotheses. Therefore, a major advance that would have implications for both the therapeutic benefit ratio and the efficiency of clinical trial execution would be a better characterization of the group of patients more likely to respond.

At present, there are relatively few clues with regard to selection of potentially responsive patients. Retrospective analyses of patients with renal cell carcinoma who have undergone IL-2 therapy suggest that patients who have only pulmonary metastases, who have undergone previous nephrectomy, and who do not have bulk disease are more likely to respond (9). The study of IL-2 therapy-induced changes in peripheral blood parameters, including rebound lymphocytosis and levels of induced LAK cell activity, has not yielded clues with regard to selection of potentially responsive patients (10). Although some data suggest that patients with pre-existing antithyroid antibodies are more likely both to develop hypothyroidism and to respond as a result of IL-2–LAK therapy, this observation needs to be extended to larger groups of patients (11). Investigators from the Cetus Corporation (Emeryville, Calif) presented data at the Biologics Advisory Committee meetings to suggest that the benefit from IL-2 therapy in patients with renal cell carcinoma may be concentrated in those patients in risk group I as defined by Elson et al. (12); if confirmed, this hypothesis may provide a useful first step toward the selection of a potentially more responsive patient cohort.

There is no substantial published information concerning other patient or tumor-related characteristics that serve as useful prognosticators of response. Potential candidates for study might include such characteristics as the major histocompatibility complex-linked phenotype of the patient, the effect of the presence of serum or tumor-associated suppressive factors (13), or the expression on tumor cells of particular antigens associated with likelihood of response, as has been described for interferon α in the treatment of renal cell carcinoma (14).

In addition, to obtain a fuller understanding of the biologic basis of this therapy in order to allow more rational therapeutic development, we need to emphasize clinical–biologic correlative studies of IL-2 combinations rather than purely empirical trials. These studies could include administration of a common active IL-2 regimen to a relatively large number of patients characterized in detail with respect to individual patient and tumor features. Given the lack of correlates that have emerged to date, these studies might include only patients with the most favorable Eastern Cooperative Oncology Group prognostic classification (12); ancillary laboratory studies might focus on such parameters as patient immune-response-gene phenotyping or other genetic markers. Tumors would be characterized prior to initiation of therapy with respect to such characteristics as expression of tumor-related antigens, major histocompatibility complex class I and II expression, and degree of lymphocyte infiltration as well as phenotypic and functional characterization of these lymphocytes. In these or other studies, patients in whom it is possible could undergo tumor biopsies during and after therapy, to allow a description of the effects of therapy on tumor immunobiology. Serial plasma samples might similarly be used to analyze therapy-associated effects, including quantitative analysis of the induction of such cytokines as tumor necrosis factor in each patient. In all cases, serial plasma, peripheral, and tumor lymphocyte populations as well as tumor specimens would be stored for future characterization of as yet undetermined possible correlates of response or resistance.

In summary, IL-2 by a variety of doses and schedules, alone or together with other cytokines or ex vivo activated cells, reproducibly results in objective clinical responses, often of prolonged duration, in patients with metastatic renal cell carcinoma and in patients with malignant melanoma. Yet fundamental questions regarding mechanisms of response and resistance and the relationship of these mechanisms to the pathophysiology of clinical toxicity remain unanswered. The failure to substantially improve response rates since publication of the original clinical results is testimony to the complexity of the biologic issues involved in the treatment approach. In addition, it illustrates the difficulties involved in conducting accurate clinical tests of preclinical hypotheses. A major challenge to further therapeutic progress with IL-2 is the identification of relatively biologically homogeneous groups of patients on whom to conduct efficient and therapeutic trials that are accurate tests of hypotheses. Further investigative strategies designed to correlate the information on the patient and tumor biology to tumor response to therapy are required. Until this type of information is available, the rational development of IL-2 therapy will be difficult, and therapeutic progress will be slowed.

References


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