INHIBITION OF INTERLEUKIN-2-INDUCED TUMOR NECROSIS FACTOR RELEASE BY DEXAMETHASONE: DOES IT REDUCE THE ANTITUMOR THERAPEUTIC EFFICACY?

To the Editor:

In a recent communication, Mier et al report that the concomitant administration of dexamethasone (Dex) increased the maximum tolerated dose (MTD) of interleukin-2 (IL-2) approximately threefold and markedly reduced the hypotension and organ dysfunction ordinarily observed in patients undergoing immunotherapy with IL-2 for advanced cancer. In a previous study Vetto et al have also pointed out that corticosteroid-treated patients were able to tolerate more IL-2, yet experienced significantly less toxicity. However, they have also noticed that none of their six patients treated with Dex, IL-2, and LAK cells showed no objective tumor regression compared with nine such responses in the control group of 27 patients who received no Dex. Thus, a concern that the reduction in IL-2 toxicity might also be associated with reduction in the therapeutic efficacy of IL-2 has been raised.

Of the 19 patients treated by Mier et al on the IL-2/Dex protocol, only one patient had a partial response (PR) while two others showed a minimal response (MR). MR (25% to 50% reduction of measurable disease) is not reported as an objective response by most investigators. Most studies would consider either a complete regression (CR) or a partial regression (> 50% shrinkage of measurable disease) as an objective response. Thus, the response rate in the small group of patients reported by Mier et al would be estimated at 5%. Rosenberg et al, who developed the original IL-2 regimen, have also gathered the greatest experience. They have reported an objective regression of cancer (partial or complete response) in 20% to 35% of 652 patients with selected advanced metastatic cancer. Their results are consistent with those of other investigators who have treated cancer patients with various protocols involving administration of high-dose IL-2; ie, 5% to 10% of IL-2-treated patients will respond completely and an additional 10% to 20% will achieve a PR.

In addition, animal experiments have shown that the administration of steroids to tumor-bearing mice abrogated the in vivo antitumor effect of IL-2. These data, connected with the low response rate observed in the few patients who received corticosteroid therapy in conjunction with high-dose IL-2, should cause apprehension regarding the addition of steroids to patients undergoing immunotherapy with IL-2. Moreover, animal and human studies have established that the response rate is directly related to the given dose of IL-2. Thus, because the concurrent administration of Dex and IL-2 permitted the use of threefold higher doses of IL-2 (1.8 \times 10^6 IU/kg compared with 6.0 \times 10^5 IU/kg, which is the MTD for IL-2 administered without steroids), one would expect a higher response rate rather than the lower rate that was noticed by Vetto et al and Mier et al. Indeed, some key questions regarding mechanisms of response and their relationship to the pathophysiology of clinical toxicity remain unsolved and it is not clear yet whether toxicity is a necessary concomitant of the beneficial antitumor effect. Until we have the answers to these questions we believe that the use of corticosteroids in conjunction with IL-2 in patients with advanced cancer should be undertaken with caution.

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REFERENCES


RESPONSE

The purpose of our interleukin-2 (IL-2)/dexamethasone study was to determine if the concomitant administration of steroids would suppress the release of tumor necrosis factor (TNF) that would otherwise occur after an injection of IL-2 and if this were demonstrated, to determine the biologic consequences of TNF suppression on various hemodynamic and metabolic parameters affected by IL-2 treatment. In this investigation, we confirmed that steroids do indeed suppress TNF production. In addition, we observed several important corollaries to the suppression of secondary cytokine synthesis such as the failure to generate a hepatic acute-phase response with increased serum C-reactive protein levels or to develop a neutrophil chemotactic defect, both of which are characteristic of patients undergoing IL-2 treatment. The clinical trial that provided the patients for the study ultimately published in the aforementioned Blood report (vol 76, page 1933, 1990) was designed with a typical phase I dose escalation format and, as such, was not tailored to address the important issue of tumor response. The IL-2 dose administered to the patients participating in this study ranged from 25,000 to 400,000 U/kg (1.5 x 10^5 to 2.4 x 10^6 IU/kg) with only a fraction of the patients receiving the maximal tolerated dose. Furthermore, many of the patients had gastrointestinal tract primaries not known for their responsiveness to immunotherapy. Since the tumor response to IL-2 is known to be dose dependent, the overall response rate in a study of this type, as computed by Dr Shiloni, has limited clinical significance. Such a determination should not be used to compare the results of this regimen, in which the IL-2 dose varied widely, with those of phase II and III studies involving a fixed IL-2 dose. Although we briefly mentioned the fact that one of our patients responded to the IL-2/dexamethasone combination, we did not intend to imply that this regimen was superior to conventional high-dose IL-2 (without steroids). In fact, we share with Dr Shiloni his concern that the reduction in toxicity associated with the addition of dexamethasone to an IL-2-based regimen may be associated with a parallel decline in efficacy with no net gain in therapeutic index. This important issue was simply not addressed in our phase I study and its resolution would require a randomized clinical trial.

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Inhibition of interleukin-2-induced tumor necrosis factor release by dexamethasone: does it reduce the antitumor therapeutic efficacy?  [letter; comment]

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