IMMUNOMODULATION IN CANCER PATIENTS TREATED WITH INTERLEUKIN-2. INDUCTION OF NON-SPECIFIC AND SPECIFIC IMMUNE RESPONSES

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1. Introduction

With the discovery of the lymphokine-activated killer (LAK) cell phenomenon, a new type of tumor-killing cells that are easily obtained and expanded in the laboratory and show a broad reactivity against a variety of different tumors became available for cancer therapy (Grimm et al., 1982).

After several years of experimental and clinical studies, it is now established that a proportion of advanced cancer patients, especially those with melanoma or renal metastatic cancers, respond to treatment with interleukin-2 (IL-2) plus LAK cells or even IL-2 alone (Rosenberg et al., 1989). The results of those studies are summarized in Table 1. On the basis of these data and on the possible survival advantage observed in renal cancer patients treated with IL-2, such a treatment has been proposed as routine of advanced renal cancer patients (Negrier et al., 1992). IL-2 has also been given the permission to be sold as effective drug in renal cancer patients in several European countries and in the USA. However, whether this treatment has to be considered more effective than other combined therapeutic modalities (e.g. IFN-α plus chemotherapy) or could be even improved by combining IL-2 with IFN-α (see Rosenberg, 1991), awaits the results of further controlled phase III clinical trials.

It is also known that adoptive immunotherapy with IL-2 at high doses is accompanied by a significant toxicity which may affect different organs and requires a considerable logistic and economic effort to be dealt with, although toxic effects reverse spontaneously upon cessation of IL-2 administration (Marolda et al., 1987; Margolin et al., 1989; Rosenberg et al., 1989). Toxicity of IL-2 is dependent on the amount used, although subcutaneous (s.c.) or
continuous infusion (c.i.) vs bolus administration has been claimed to result in a lower toxicity (West et al., 1987; Atzpodien et al., 1990). However, when equal amounts of IL-2 were given by bolus and by c.i., no significant difference in toxicity was found, although IL-2 given by c.i. resulted in more evident biological effects like lymphocytosis or LAK activation (Weiss et al., 1989).

**TABLE 1**
Clinical results of treatment of advanced cancer with IL-2 plus LAK or IL-2 alone

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Treatment</th>
<th>IL-2</th>
<th>IL-2/LAK</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Evaluable</td>
<td>Evaluable</td>
</tr>
<tr>
<td>Renal</td>
<td>IL-2</td>
<td>54</td>
<td>72</td>
</tr>
<tr>
<td>Melanoma</td>
<td>IL-2</td>
<td>42</td>
<td>48</td>
</tr>
<tr>
<td>Others*</td>
<td></td>
<td>33</td>
<td>21</td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response. *Include lung, breast, colon cancers and non-Hodgkin lymphomas.

IL-2 treatment can induce *in vivo* lymphocyte proliferation, the development of broad cytotoxicity named LAK activity (Gambacorti-Passerini et al., 1988) and the rise in some serum markers, such as soluble CD25 (Gambacorti-Passerini et al., 1990). Unfortunately, no parameter has been consistently and strongly enough associated to clinical response in order to select responding patients from non-responding ones. In conclusion, the IL-2/LAK therapy has provided numerous important findings on the mechanism of *in vivo* immune modulation although we still ignore why only a fraction of patients can respond to treatment. The low percentage of response observed in most studies (10-30%) remains the major limitation to a wider clinical use of IL-2.

We will now examine the immunobiological modifications exerted by *in vivo* IL-2 administration to see whether this treatment can activate both non-specific and tumor-specific immune reactions and whether their variable activation may explain different therapeutic effects.