Editorial

Interleukin-2 and Cancer – Physiological and Pharmacological Uses

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For many years papers in *Folia Biologica* have contributed substantially to treatment of advanced cancer with hormones of the immune system, describing how to make the best possible use of interleukin-2 (IL-2) and other cytokines. An early major focus was on local application, which was not used initially in patient therapy.

In 1985, Steven Rosenberg described the first clinical results of the systemic use of IL-2 in patients with advanced metastatic cancer (Rosenberg et al., 1985). High-dose bolus intravenous application of IL-2 – "pharmacologic" doses – led to breath-taking success, including complete and long-lasting responses in metastatic renal-cell cancer and advanced melanoma – in which no treatment had been available before. That success, unfortunately, took a great toll: the toxicity of the therapy, including a 4% treatment-related death rate, was considerable (Lotze et al., 1986), requiring stringent selection of patients and leaving most with no treatment option.

The bad reputation of IL-2 treatment reflects a historical misunderstanding and an underestimation of the considerable potential of this immune hormone. The major toxicity of IL-2 is directly – and nearly exclusively – linked to intravascular IL-2 concentrations (Cotran et al., 1988). However, the major antitumour activity of IL-2 depends on the activation of immune cells, preferably local immune cells like tumour-infiltrating lymphocytes (Rosenberg et al., 1988; Topalian and Rosenberg, 1990). Bubeník (1983) was the first to describe the ability of IL-2 to activate cytotoxicity in tumour-associated lymphocytes and to suggest local IL-2 application in cancer patients (Bubeník et al., 1983), and he reported successful use in mice (Bubeník et al., 1986). Vaage in 1987 described the influence of the administration schedule on the therapeutic effect of IL-2 (Vaage et al., 1987). Pizza (1984) injected interleukin-2 preparations directly into tumours with therapeutic success and no toxicity (Pizza et al., 1984), and Forni (Forni et al., 1986; Cortesina et al., 1989) reported the effectiveness and good tolerance of local and perilymphatic application of IL-2, pointing to an additional way to avoid intravascular IL-2 concentrations and the toxicity associated with it. Animal use confirmed the effectiveness and tolerance of local IL-2 (Den Otter et al., 1991). In 1987, Ottow suggested intraperitoneal use of IL-2 in the treatment of malignancy that spreads onto peritoneal surfaces by implantation (Ottow et al., 1987). In humans, continuous high-dose IL-2 bladder perfusion led to distinct local immune modulation and measurable antitumour responses without toxicity (Huland and Huland, 1989; Huland and Huland, 1992). That has encouraged our group to use inhaled IL-2, which is now a successful and well-tolerated treatment for lung metastases of different origins (Huland et al., 1994; Heinzer et al., 1999; Petzold et al., 1999; Enk et al., 2000). The important finding of the early studies of local IL-2 application is that toxicity can be separated from effectiveness. Mimicking the physiological action of IL-2 results in effective treatment with little or no toxicity.

As a result of detailed studies on IL-2, it is now established that only three variables determine T-cell G1 progression to DNA replication: IL-2 concentration, IL-2 receptor density, and the duration of the IL-2 receptor interaction (Smith, 1988). All are variables of the local immune response and local T-cell proliferation. T-cell clonal proliferation after antigen challenge is obligatory for immune responsiveness and immune memory, and the IL-2 T-cell system has opened the way to a molecular understanding of phenomena that are fundamental to biology, immunology, and medicine (Smith, 1988). There is a good chance that IL-2 represents a general model to teach us important principles of using cytokines physiologically in the regulation of immune responses to treat diseases successfully.

Local (physiological) use and systemic (pharmacological) use of IL-2 are not mutually exclusive; both could be very appropriate in metastatic cancer. Local physiological therapy intensifies treatment without intensifying toxicity. The dosage and duration of systemic application have to be tailored to the general

Received April 26, 2001.

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health status of the patient and may be limited to a relatively short treatment time. Local physiological applications in high doses are well tolerated over the long-term therapy in nearly all patients and are quite independent of stringent patient selection.

Immunotherapy today is one of the pillars of cancer treatment in addition to operation, chemotherapy, and radiotherapy. Changing the mode of application might not sound spectacular but for many patients it makes the difference between benefitting from IL-2 therapy and being excluded from it.

With that perspective in mind, one can hope that in the near future patients with incurable metastatic disease will be included more and more in protocols that use well-tolerated immunotherapy alone or in combination with chemotherapy and not just in chemotherapy protocols alone.

The future of cytokine therapy is promising. The physiological use of the many immune hormones will provide us with invaluable tools for treating cancer and other diseases while maintaining a high quality of life.

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