A Comparison of Systemic Versus Inhaled Recombinant IL-2 Administration for the Treatment of Metastatic Renal Cell Carcinoma

(carcinoma / renal cell / interleukin-2 / interferon-α / survival / objective response / toxicity / inhalation)

E. HULAND, H. HEINZER, H. HULAND

Department of Urology, University Hospital Hamburg-Eppendorf, Germany

Abstract. The aim of the current study was to compare the objective response and survival rates of patients with mRCC treated with IL-2 administered either systemically (SYST, subcutaneously) or via inhalation (INH), using relatively large sample sizes to afford a more meaningful comparison. We used univariate and multivariate analyses to retrospectively evaluate the data from two different databases generated from 277 patients treated with IL-2 during the 1993-1997 period, one developed at the University Hospital Hamburg-Eppendorf, and the other at Chiron-Amsterdam. Patients treated with INH IL-2 tended to have a poorer ECOG performance status than patients receiving SYST IL-2. Of 75 patients receiving INH IL-2, eight (10.7%) achieved an objective response; of 202 patients administered SYST IL-2, 45 (22.2%) achieved an objective response. The median survival time was 13.8 months for patients receiving INH IL-2 and 13.1 months for patients treated with SYST IL-2. One- and two-year survival rates were also comparable for the two treatment modalities (one-year: INH, 55%; SYST, 56%; two-year: INH, 28%; SYST, 26%). There was no significant difference in the likelihood of survival for patients receiving INH IL-2 versus SYST IL-2 (risk ratio = 0.82, P = 0.27). Patients administered INH IL-2 experienced considerably less toxicity and complications than patients administered SYST IL-2. We conclude that INH IL-2 treatment is at least as effective as SYST IL-2 treatment in promoting the survival of patients with mRCC. Given that INH IL-2 treatment of patients with a poorer ECOG performance status elicited a survival rate comparable to that seen with SYST IL-2 treatment of patients with a superior performance status, the potential exists for INH IL-2 treatment to be even more effective for patients having a better performance status. Additionally, INH IL-2 treatment is considerably less toxic and associated with fewer complications than SYST IL-2 treatment, thus providing a therapeutic option for otherwise untreatable patients, offering patients a relatively good quality of life, and requiring fewer co-medications. Nonetheless, selection of an IL-2 treatment modality should be based on several patient-related considerations. Moreover, these two IL-2 treatment modalities need not be mutually exclusive.

Interleukin (IL)-2, historically referred to as T-cell growth factor, is a 15 kD glycoprotein synthesized and secreted by activated T lymphocytes. It is also the principal soluble factor responsible for proliferation of these cells via activation of high-affinity IL-2 receptors (Bubeník, 1990; Kolitz and Mertelsmann, 1991). In animal models and in humans, IL-2 administration can have antitumor effects. These effects may be mediated, at least in part, by stimulating host immune defenses (Bubeník, 1983; Bubeník, 1990; Kolitz and Mertelsmann, 1991; Foa et al., 1992). IL-2 induces proliferation of specific tumor-reactive, IL-2 receptor-bearing T cells (i.e., cytolytic T lymphocytes [CTL], T helper cells, T suppressor cells) as well as cells with less specific, but still distinct tumor-reactive cytolytic activity (i.e., natural killer [NK] cells and lymphokine-activated killer [LAK] cells). Additionally, IL-2 enhances NK cell-mediated cytolysis of tumor cells, induces differentiation of LAK precursor cells into cytotoxic, tumor-reactive killer cells, and stimulates secretion of other soluble mediators, including tumor necrosis factor-α (TNF-α). These biological effects of IL-2 provide the rationale for using IL-2 as a treatment for cancer. Based on early clinical studies of IL-2 treatment of cancer, the most favorable results have been documented consistently for metastatic renal cell cancer (mRCC) and melanoma (Foa et al., 1992).

Metastatic renal cell carcinoma does not respond well to conventional chemotherapy, radiation therapy or hormonal treatment. In contrast, patient objective response rates following administration of high-dose IL-2 via intravenous bolus or continuous infusion have been reported to be as high as 30% (Atzpodien et al., 1990a; Whitehead et al., 1990; Koretz et al., 1991; Lissoni et al., 1992; Sleijfer et al., 1992; Atzpodien et al., 1993b; Buter et al., 1993; Lissoni et al., 1993; Palmer et al., 1993; Lissoni et al., 1994; Angevin et al., 1995; Law et al.,

Received August 30, 2000.

Corresponding author: Edith Huland, Head, Transplantation- and Tumorimmunology, Urologische Klinik und Poliklinik, Universitäts-Krankenhaus Eppendorf, University of Hamburg, Martinistr. 52, 20246 Hamburg, Germany. Tel.: 49 (40) 42803-4424; Fax: 49 (40) 42803-4662; e-mail: huland@uke.uni-hamburg.de.

Abbreviations: CD – complete response, CI – confidence interval, ECOG – Eastern Cooperative Oncology Group, DTI – diagnosis-to-treatment interval, IFN-α – interferon-α, IL-2 – interleukin-2, INH – inhalation(al), inhaled, mRCC – metastatic renal cell carcinoma, PD – progressive disease, PR – partial response, SD – stable disease, SYST – systemical(ly).

1995; Lissoni et al., 1995; Tourani et al., 1996; Figlin et al., 1997). Furthermore, patient survival rates at one and two years following treatment were substantially greater than expected for the untreated patient population (Figlin et al., 1997). However, the toxicity elicited by high doses of IL-2 is a major treatment issue and limits the candidate patient population. Well-known side effect of IL-2 administration include fever, fatigue and malaise. Additionally, high-dose IL-2 treatment can cause a pulmonary vascular leak syndrome, which may lead to potentially fatal respiratory failure in some patients (Lee et al., 1989).

Treatment of mRCC with subcutaneous IL-2, administered alone or in combination with interferon-α (IFN-α), appears to be as effective as intravenous high-dose IL-2 administration, but is associated with considerably lower toxicity (Atzpodien et al., 1990a; Atzpodien and Kirchner, 1991; Atzpodien et al., 1993a; Atzpodien et al., 1993b; Lissoni et al., 1993; Palmer et al., 1993; Ravaud et al., 1994; Vuoristo et al., 1994; Atzpodien et al., 1995; Marincola et al., 1995; Buzio et al., 1997). This finding suggests that alternative routes of IL-2 administration and/or different dosing regimens may influence IL-2 treatment efficacy and safety, and consequently, patients' quality of life.

Local IL-2 administration has been investigated as an alternative to the systemic treatment of mRCC. Local routes of administration offer the potential for delivery of effective IL-2 concentrations directly to tissues. When IL-2 was administered locally via interstitial injection or organ-specific routes, treatment responses were observed accompanied by a more favorable toxicity profile (Huland and Huland, 1989; Steis et al., 1990; Astoul et al., 1994). Indeed, objective response rates for patients with pulmonary mRCC treated with INH IL-2 have ranged from 15% to 60% (Huland et al., 1994; Lorenz et al., 1996; Huland et al., 1997). Moreover, INH IL-2 treatment considerably prolonged patient survival from that predicted according to risk factors (Huland et al., 1992; Huland et al., 1994; Huland et al., 1997). In addition, the use of INH IL-2 as a second line therapy has been successful in patients with mRCC and other primary tumors (Enk et al., 1997; Petzoldt et al., 1999; Roigas et al., 1999). In this regard, pulmonary metastases of melanoma as well as breast and ovarian carcinomas responded to INH IL-2 therapy with similar rates in patients previously unsuccessfully treated with systemic chemo- or immunotherapies (Enk et al., 1997; Petzoldt et al., 1999; Roigas et al., 1999).

The objective of the current study was to compare the objective response and survival rates of patients with mRCC treated with IL-2 administered either systemically or via inhalation, using relatively large sample sizes to afford a more meaningful comparison. To this end, we used univariate and multivariate analyses to retrospectively evaluate the data from two different databases generated from patients treated with IL-2 during the 1993-1997 period, one developed at the University Hospital Hamburg-Eppendorf, and the other at Chiron-Amsterdam.

Material and Methods

Study design

This was a retrospective analysis of therapeutic outcome data collected prospectively from patients treated with either INH (n = 75) or SYST (n = 202) IL-2.

Patients

Patients were enrolled between 1993 and 1997 for treatment with INH or SYST IL-2. The studies in which the patients were enrolled were approved by the review boards of the Klinikum Steglitz – Free University of Berlin, the University of Hamburg, and the Paris Necker Enfants-Malades. Informed written consent was given by each patient before enrollment.

(a) *Inclusion criteria.* Patients receiving INH IL-2 therapy were males or females at least 18 years of age. These patients had histologically confirmed renal cell carcinoma and documented progressive pulmonary or mediastinal metastases.

Patients receiving SYST IL-2 therapy were at least 18 years of age with a histologically confirmed diagnosis of renal cell carcinoma and documented progressive disease. Patients had organ function sufficient to meet the requirements specific to each of the individual study protocols, as summarized in Table 1 (Atzpodien et al., 1990b; Sleijfer et al., 1992; Ravaud et al., 1994; Tourani et al., 1996).

(b) *Exclusion criteria.* Patients were not enrolled for INH IL-2 treatment if they did not have progressive disease, had an Eastern Cooperative Oncology Group (ECOG) performance status score of 4 (this latter group of patients, usually not treated, benefits in terms of survival from non-toxic immunotherapy) (Huland et al., 2000), or presented with clinically significant cardiac disease, serious active infection (including human immunodeficiency virus infection and infectious hepatitis), or inoperable central nervous sytem metastases. Patients with organ allografts, likely to require corticosteroids, or with pre-existing autoimmune disease were also excluded. No further patient selection was performed.

Patients were not eligible to receive SYST IL-2 treatment if they met exclusion criteria specific to each of the study protocols, as summarized in Table 1 (Atzpodien et al., 1990b; Sleijfer et al., 1992; Ravaud et al., 1994; Tourani et al., 1996).

Treatment with IL-2

(a) *INH IL-2 therapy.* The treatment was performed as published previously (Huland et al., 1997). In brief, 18–36×10^6 IU IL-2 were given as a daily dose. Ninety percent of the dose ($16.4–32.7 \times 10^6$ IU) were given by INH as five separate applications daily, and 10% ($1.6–3.3 \times 10^6$IU) were given by subcutaneous injection. The treatment was performed exclusively on an outpatient basis. INH of IL-2 was performed with a Salvia