

Table 7. Toxicity experienced during IL-2 treatment.

Toxicity grade	INH IL-2 treatment (n = 75)	SYST IL-2 treatment (n = 202)
Grade 1 (%)	93	95
Grade 2 (%)	97	94
Grade 3 (%)	24	46
Grade 4 (%)	0	3

INH IL-2 treatment did not require medications for the treatment of systemic side effects.

Fever, flu-like symptoms and anorexia were the most common Grade 3 and Grade 4 events experienced by patients treated with SYST IL-2. Other adverse events were predominantly Grade 1 or Grade 2 in severity. Patients treated with SYST IL-2 received antipyretic medications prophylactically. Antiemetic and antidiarrheal medications were administered as required during SYST IL-2 therapy.

Discussion

There is a growing consensus that objective antitumor responses may not be the critical endpoint to be used when evaluating the efficacy of antitumor therapy. A slow rate of tumor growth, manifested as an inhibition of disease progression, may also benefit the patient. Thus, the patient survival and performance status may ultimately be more important measures of antitumor efficacy (American Society Clinical Oncology (ASCO), 1996; Buzio et al., 1997).

The prognosis of patients with mRCC is poor. Without immunotherapy, the median length of patient survival is less than 7 months. Patients with mRCC who have been highly selected for a combination of the most favorable prognostic factors have a median survival time of 12.8 months (Elson et al., 1988).

In the present retrospective study, the two IL-2 treatment schedules resulted in almost identical survival times of 13.8 months for patients receiving INH therapy and 13.1 months for patients receiving SYST therapy. This is a striking finding because two widely accepted predictive factors for patient survival, ECOG performance status and objective response rate, were different for the two treated groups of patients. Of those patients receiving INH IL-2, 40% were characterized by an ECOG score that was one grade lower than that characterizing patients treated with SYST IL-2. According to Elson and colleagues (1988), this observation should have been accompanied by a reduction of several months in the survival time of the 40% of patients treated with INH IL-2.

In the current analyses, the overall objective response rates were 10.7% for patients treated with INH IL-2 and 22.2% for patients receiving SYST IL-2 therapy. Based on these data, comparable survival rates for patients receiving INH versus SYST IL-2 would not be antici-

pated. However, the proportions of patients with progressive disease in each of the two treatment groups were almost identical, 40% and 39.1% of patients treated with INH IL-2 and SYST IL-2, respectively. Thus, these data show that both INH and SYST IL-2 treatment regimens can effectively prevent disease progression, and strongly suggest that stable disease is meaningful for the survival of patients with mRCC receiving immunotherapy. Notably, stable disease for patients receiving INH IL-2 treatment was defined as a stabilization persisting for at least 3 months, a definition that differs markedly from the WHO criteria for stable disease. Stable disease may be supported by the long-term treatment schedule employed to treat patients with INH IL-2. Typically, INH IL-2 treatment is administered continuously until disease progression is observed, based on the rationale that treatment is administered for as long as the tumor is present. In contrast, stable disease for patients receiving SYST IL-2 therapy was defined as a stabilization persisting for at least 4 weeks, in accordance with the WHO criteria. SYST IL-2 treatment is cyclic and is not given continuously because of the development of side effects. Our observation is consistent with data published by Figlin and colleagues (1997), showing that the survival of patients with stable disease was significantly better than that of patients who manifested progressive disease, and similar to that of patients having achieved a partial response.

The objective response rates determined by the current analyses are consistent with the range of responses reported previously for the IL-2-mediated treatment of mRCC. In two earlier analyses, we found response rates for the INH IL-2 treatment of mRCC of 15% and 60% (Huland et al., 1994; Huland et al., 1997). However, the latter was based on a relatively small sample size of only 15 patients. Lorenz and coworkers (1996) described a response rate of 21% for patients treated with INH IL-2. Similarly, patients with mRCC treated with SYST IL-2 manifest response rates that range from 0% (Koretz et al., 1991; Angevin et al., 1995) to 30% (Lissoni et al., 1993).

Patients treated with INH IL-2 versus SYST IL-2 were characterized by similar survival rates. At one year, the survival rates were 55% for patients in the INH IL-2 group and 56% for patients in the SYST IL-2 group. At two years, the survival rates had decreased by one half, being 28% for the patients receiving INH IL-2 and 26% for patients treated with SYST IL-2. These findings are consistent with previously published observations. Figlin

et al. (1997) reported that the one- and two-year survival rates for patients with mRCC treated with systemic IL-2 were 61% and 40%, respectively. Similarly, Henriksson et al. (1998) found that 65 patients with mRCC had a 40% survival rate one year after treatment with very low dose SYST IL-2 in combination with IFN- α and tamoxifen.

The lack of a difference in survival rates between patients treated with INH IL-2 and patients receiving SYST IL-2 therapy is of interest for two reasons. First, similar survival rates were observed despite the fact that INH IL-2 and SYST IL-2 elicited different complete and partial responses in the treated patients. Thus, objective response rates may not predict survival, and lower response rates may not disadvantage patients with respect to survival. Indeed, long-term stabilization of disease with long-term IL-2 treatment obviously helps to prevent disease progression and contributes to increased patient survival. Second, similar survival rates were observed for the two IL-2 treatment groups, despite the fact that patients receiving INH IL-2 therapy had an overall poorer performance status (i.e., higher ECOG score) than patients receiving SYST IL-2 treatment. Thus, even patients with mRCC who are more severely ill may benefit from IL-2 treatment.

Multivariate analysis of patient survival using the Cox's proportional hazards model revealed that patients treated with INH IL-2 versus SYST IL-2 had a comparable likelihood of survival (risk ratio = 0.82, $P = 0.27$). However, patients with risk factors did have a lower likelihood of survival than those patients without risk factors, regardless of the IL-2 treatment modality. Thus, patients with a poorer performance status/higher ECOG score had a lower likelihood of survival with IL-2 treatment than patients with a better performance status/lower ECOG score. The performance status has been found to be a good prognostic indicator of IL-2 treatment benefit (Lissoni et al., 1994). A poor performance status may predict decreased IL-2 treatment benefit because it may reflect a compromised function of all biological systems, including the immune system (Lissoni et al., 1994).

Use of IL-2 combination therapy does not appear to consistently enhance the antitumor activity of IL-2. For example, SYST IL-2 used in combination with LAK cell infusion was reported to elicit response rates ranging from 3% to 40% (Escudier et al., 1994; Law et al., 1995; Kruit et al., 1997). Similarly, IL-2/IFN- α combination therapy was associated with response rates between 15% (Vuoristo et al., 1994) and 31% (Atzpodien and Kirchner, 1991). In the current study, 68% of patients treated with SYST IL-2 received combination therapy with IFN- α , whereas only 40% of patients treated with INH IL-2 received IFN- α concomitantly. Although substantially more patients in the SYST IL-2 group than in the INH IL-2 group received combination therapy with IFN- α , and the SYST IL-2 group experienced a higher objective response rate than the INH IL-2 group, the SYST IL-2 group did not have a longer survival time or a greater

survival rate (see below) when compared with the INH IL-2 group. Consistent with this observation, Negrier and colleagues (1998) also reported that a higher objective response rate to immunotherapy did not lead to a longer survival time for patients with mRCC. These findings suggest that, for the treatment of mRCC, IFN- α does not increase the antitumor activity of IL-2.

The clinical benefit associated with IL-2 treatment of mRCC presumably reflects, at least in part, the effect of IL-2 on the immune system. When administered subcutaneously, IL-2 increases eosinophilia and lymphocytolysis, which may be related to an IL-2-mediated IL-5 release (Angevin et al., 1995). Similarly, INH IL-2 results in an expansion of pulmonary immunocompetent cells, including eosinophils (Lorenz et al., 1996). Interestingly, Lissoni and colleagues (1995) recently reported that the efficacy of IL-2 was reduced in patients with mRCC who were characterized by abnormally high plasma levels of insulin-like growth factor-1 (IGF-1). However, it is unclear whether the IGF-1 levels simply mirror the extent of the disease, or whether they play a role in the antitumor action of IL-2.

The toxicity experienced by patients receiving INH IL-2 or SYST IL-2 treatment in the current study differed dramatically. Although the proportion of patients experiencing Grade 1 and Grade 2 toxicities was comparable between the two groups, twice as many patients treated with SYST IL-2 as those treated with INH IL-2 experienced Grade 3 toxicity. Furthermore, no patient receiving INH IL-2 experienced Grade 4 toxicity, while 3% of patients receiving SYST IL-2 did experience this degree of toxicity. Thus, INH IL-2 treatment is as effective as SYST IL-2 in promoting the survival of patients with mRCC, but less toxic.

The toxic responses evoked by IL-2 treatment may reflect the IL-2-mediated induction of inflammatory cytokines. In particular, IL-2 administered systemically may initiate a cascade of inflammatory cytokines, such as TNF- α , during its passage in the circulation (Gemlo et al., 1988).

Toxicity associated with IL-2 therapy is important when considering individual patient treatment needs. Patients with serious comorbidity are not good candidates for SYST IL-2 therapy, because they are less able to tolerate the more severe toxicity associated with this treatment modality. However, effective IL-2-based treatment schedules are not necessarily associated with toxicity. Indeed, IL-2 that is inhaled may be a more attractive treatment modality for high-risk patients, because it is considerably less toxic but just as effective as SYST IL-2 therapy. Notably, low toxicity is a prerequisite for long-term treatment with IL-2.

The quality of life with various IL-2 treatment modalities should also be considered carefully when determining the optimal therapeutic approach for a particular patient with mRCC (Heinzer et al., 1999). For some patients, short, intensive treatment with SYST IL-2 that