Nitrate Plasma Level as a Marker of Nitric Oxide Production After Subcutaneous Interleukin 2 Immunotherapy

Interleukin 2 (IL-2) schedules were initially developed with the use of chemotherapy guidelines in which the maximum tolerable dose was given by intravenous bolus or continuous infusion over a few days; however, despite encouraging clinical results, relevant cardiovascular effects were common [1] and frequently required hospitalization of the patient in the intensive care unit. This kind of toxicity represents the main dose-limiting effect of IL-2 immunotherapy, and evidence has increased that nitric oxide (NO) may contribute to the adverse effects through its vasodilator properties [2–4]. Subsequently, Atzpodien et al. [5] demonstrated that subcutaneous administration of IL-2 at low doses is clinically effective and causes no severe cardiovascular toxicity. More recently, Buzio et al. [6] demonstrated that very low doses of subcutaneous IL-2 can induce major and persistent immunologic effects, with an extremely safe toxicologic profile.

Using a sensitive high-performance liquid chromatography method [7], we studied the NO stable end product nitrate (NO3) in the plasma of 11 patients with advanced renal cell carcinoma who were receiving IL-2 (the protocol of Atzpodien et al.) and of seven patients with renal cell carcinoma who were enrolled in a national multicenter adjuvant study of very low dose, subcutaneous IL-2 (the protocol of Buzio et al.). After we obtained written informed consent from the patient, blood samples were drawn early in the morning after the subjects had fasted overnight, before and after the first treatment cycle; in the protocol of Atzpodien et al., each cycle lasted 6 weeks, and IL-2 was given at 9 MU every 12 hours for the first 2 days and then at 1.8 MU/m² every 12 hours [5], while in the protocol of Buzio et al., each cycle lasted 4 weeks and IL-2 was given at 2 MU/m² the first 2 days of each week and at 1 MU/m² thereafter [6]. In both protocols, interferon alfa was also given intramuscularly.

In the patients treated by use of the schedule of Atzpodien et al., the mean NO3 titers were 32.03 μM (±7.86 standard deviation [SD]; range: 18.72–42.76 μM) before treatment and 79.01 μM (±13.38 SD; range: 47.83–94.73 μM) after treatment; the differences between pretreatment and post-treatment NO3 titers were statistically significant (P = .003 by Wilcoxon test; all results are two-sided). In patients treated with the use of the schedule of Buzio et al., the mean NO3 titers were 36.13 μM (±7.90 SD; range: 21.76–47.32 μM) before treatment and 46.02 μM (±6.56 SD; range: 36.21–56.93 μM) after treatment; this time, no statistically significant differences were found (P = .13). Our data demonstrate 163.1% (±89.0% SD) and 10.7% (±12.0% SD) increases in these values are much lower than the respective NO3 titers after the first IL-2 cycle according to the protocols of Atzpodien et al. and Buzio et al., respectively. Both of these values are much lower than the 669.7% and 935.0% increase reported by Ochoa et al. [2] for two different schedules of high-dose, intravenous IL-2.

The low rate or even the total absence of cardiovascular toxicity reported by Atzpodien et al. [5] and Buzio et al. [6], respectively, was confirmed in our patients; as a matter of fact, all patients were treated on an outpatient day-hospital basis and had sporadic and clinically insignificant blood pressure reductions, requiring neither hospitalization nor pharmacologic treatment. This safe toxicologic profile, compared with the severe systemic manifestations described in high-dose trials [9], is consistent with a lower stimulation of NO production.

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References


Notes

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