Clinical studies with biological response modifiers in the treatment of solid tumors
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
1994

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Infection after subcutaneous interleukin-2


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Introduction

High-dose IL-2 therapy given either as intravenous (IV) bolus injections or continuous infusion is associated with a high frequency of significant bacterial infections in cancer patients. Sepsis was one of the major causes of IL-2 therapy related deaths in the initial protocols (1-3). Most infections are related to indwelling central venous catheters that are in place for several days. But also changes in the host defence mechanism with a chemotactic defect in neutrophils have been reported in patients receiving IL-2 therapy (4). Recently, Jones (5) reported a high frequency of bacteriological proven infection in patients receiving subcutaneous IL-2 and Interferon-α in the absence of central venous catheters, which they attribute to IL-2 treatment. They advise careful monitoring of treatment with subcutaneous IL-2, and the investigation of the role of prophylactic antibiotics in this context. We reported earlier an outpatient regimen with single-agent subcutaneous IL-2 in patients with disseminated renal cell cancer (6). We retrospectively analyzed and report here our experience concerning the rate of infection in this regimen.

Patients and methods

Patients received daily subcutaneous injections of 18 x 10⁶ International Units IL-2 (EuroCetus, Amsterdam, Netherlands) on day 1 to 5 in the first week, while the dose in the first two days of the following weeks was reduced to 9 x 10⁶ International Units. Patients were treated for 4 or 6 weeks. Treatment was repeated after 2 to 3 weeks rest period to a maximum of 3 courses. Paracetamol 250-500 mg orally every 4 to 6 hours was given to suppress pyretic reactions. Patients visited the outpatient clinic on day 1 and 5 of every weekly cycle. Toxicity was assessed with a patient interview, physical examination, full blood counts, assessment of renal, liver, and coagulation functions. No routine blood cultures were performed. In case of clinical signs of infection appropriate cultures were taken and antibiotic
treatment was initiated.

Results

A total of 42 patients, 24 men and 18 women, mean age 59 years (range 29-76) received 468 weeks of treatment. We found clinical evidence of infection for which antibiotics were indicated on 6 occasions. (1.3%) One patient with a spinal cord lesion and atonic bladder was treated three times for recurrent urinary infections which were related to the urinary catheter. A second patient received antibiotics for a local infection with group B hemolytic streptococci in the leg which was compromised with a thrombotic venous occlusion. One patient with multiple lung metastases was treated for a clinical pulmonary infection and one patient was treated for a clinical epididymitis.

Discussion

Although no routine blood cultures were performed and asymptomatic bacteriaemia cannot be excluded, the low incidence of clinical infection in this group of 42 patients and the absence of symptoms that could be ascribed to bacteriaemia suggest that there is no indication for the use of prophylactic antibiotics in patients treated with single-agent subcutaneous IL-2. Since no excess of infection in cancer patients receiving IFNα has been reported (7,8), the relation between combination therapy with IL-2 and IFNα and infection needs further investigation.

References

Chapter 7b

Neuropsychiatric symptoms during treatment with interleukin-2

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Introduction

Neuropsychiatric changes are frequently observed during IL-2 therapy. These side effects are dose and schedule dependent. On intensive treatment regimens with intravenous administration of high-dose IL-2, patients become frequently agitated, combative, disoriented, or somnolent, and occasionally comatose (1-3). Fenner recently (4) reported neuropsychiatric symptoms during outpatient combination treatment with subcutaneous interleukin-2 at a dose of 3 x 5-20 MIU/m², and interferon-α with or without subsequent intravenous 5-fluorouracil for metastatic renal cell carcinoma in 39 of 101 patients. Treatment limiting neuropsychiatric symptoms were less frequent than in patients treated with high-dose intravenous IL-2, and symptoms resolved spontaneously after cessation of treatment, possibly indicating brain metastases. All three drugs used have their own neurotoxicity, and it is therefore difficult to attribute toxicity to one of them. We report the neuropsychiatric toxicity of an outpatient regimen of subcutaneous IL-2 monotherapy in patients with renal cell cancer (5).

Materials and methods

A total of 61 patients with progressive metastatic renal cell carcinoma were treated. Mean age was 59 years (range, 41 to 75 years) and 37 patients were male. Patients received daily subcutaneous injections of 18 x 10⁶ International Units IL-2 (EuroCetus, Amsterdam, Netherlands) on day 1 to 5 in the first week, while the dose in the first two days of the
following weeks was reduced to $9 \times 10^6$ International Units. Patients were treated for at least four consecutive weeks per course. Treatment was repeated after a 2 or 3 week rest period unless progressive disease was recorded. Paracetamol 250-500 mg orally every 4 to 6 hours was given to suppress pyretic reactions. Neuropsychiatric toxicity was evaluated every treatment week.

Results

104 treatment courses were administered. Clinically relevant neuropsychiatric symptoms were recorded in 14% of courses in 14 patients. IL-2 treatment was discontinued in 2 patients because of neurotoxicity. One patient died of brain stem ischemia after a myocardial infarction and one patient had progression of a partial spinal cord lesion due to metastases in the first week of IL-2 treatment, for which treatment was discontinued. Coma or seizures did not occur. Disorientation was noted in 2 patients; 2 had difficulties with concentration; 1 complained about hallucinatory symptoms on the second day of treatment for which IL-2 dose was temporarily reduced for one day whereupon symptoms resolved spontaneously; and somnolence occurred in 3, peripheral neuropathy in 2, and vertigo in 2 with hypotension ($p_{syst} < 100$ mm Hg). Computer tomography of the brain revealed brain metastases in 2 patients, with disorientation and depressive symptoms in 1 and headache and concentration difficulties in the other.

Discussion

Clinically relevant neuropsychiatric symptoms during this outpatient regimen with subcutaneous IL-2 monotherapy were rare and required cessation of treatment in 2% of courses. Brain metastases are not uncommon in renal cell cancer and as we found overt metastases in 14% of patients with neuropsychiatric symptoms on IL-2 these symptoms may be indicative of metastases of the brain or other central nervous system localizations.

References