Consecutive IL-2 and IFN-a2a Maintenance in a Patient with Acute Non-lymphoblastic Leukemia and Renal Cell Cancer

Akýn UYSAL, Muhit ÖZCAN, Celalettin ÜSTÜN, Semin FENKÇÝ

Ankara University, Medical Faculty, Ýbn-i Sina Hospital, Department of Haematology, Ankara, TURKEY

ABSTRACT

Over the last few years, the use of ýnterleukin-2 (IL-2) and lymphokine-activated killer (LAK) cells have been found to be effective in the treatment of some solid tumours and acute myeloid leukemia. Our patient was initially diagnosed as having bilateral synchronous renal cell cancer (RCC) and underwent nephrectomy. Approximately two years after the operation he developed leukopenia without any sign of residual renal cell cancer. Bone marrow examination revealed acute myeloblastic leukemia (AML). IL-2 following IFN-a2a was used as a maintenance therapy after a standard remission induction and a consolidation therapy. Our patient has been still disease free for 58 months after the diagnosis of AML and 71 months after the diagnosis renal cell cancer. Review of the literature showed that this is the first case who has both RCC and AML and was treated successfully with IL-2 and IFN-a2a.

Key Words: IL-2, IFN-a2a, Renal cell cancer, ANLL.

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INTRODUCTION

Although the disease-free and overall survival periods has been prolonged in acute myeloblastic leukemia (AML) with intensive postremission therapies there is still a considerable relapse rate[1]. Since the duration of the initial complete remission (CR) largely determines the duration of survival, the goal of treatment in these patients is to maintain CR by using other therapeutic strategies such as immunomodulation. IL-2, which is a T cell-derived cytokine with pleiotropic action, is capable of amplifying spontaneous cytotoxicity and of inducing lymphokine actived killer (LAK) activity[2].

Following 2-7 days preincubation with IL-2, mouse and human lymphocytes became capable of lysing allogeneic or autologous tumoral cells[2]. This cytotoxic activity is mediated by the lymphokine-activated killer cells (LAK). IL-2 and LAK cell therapy induced tumour regression in both animal models and in some patients with advanced cancer[3]. It has been shown that human leukemia blasts are also susceptible to the lytic effect of LAK in vitro[4]. IL-2 alone is capable of blocking

the growth of leukemia cells[5]. Based on these studies, IL-2 is used in various steps of the management of AML[6]. On the other hand, IL-2 has been approved to be used in the treatment of the metastatic renal cell cancer. IL-2 either alone or in combination with LAK cells have been achieved response rates as high as 25-30% in the advanced renal cell cancer[7,8].

Here we report a case, who developed renal cell cancer and consequent AML, received IL-2 and interferon-a2a for maintenance therapy after complete remission is attained.

CASE REPORT

In December, 1994 a 56-year-old man underwent right radical and left partial nephrectomy for a non-metastatic bilateral renal cell carcinoma. He did not receive chemotherapy or radiotherapy after the operation. When leukopenia was detected without any sign of renal cell cancer in March 1996, the patient was admitted to the department of Haematology. The performance status of the patient was II according to WHO classification. His laboratory examinations were as following: Hemoglobin 10.5 g/dL, hematocrite 30%, white blood cell $2.1x10^9$/L, platelet $57x10^9$/L, blood urea nitrogen 17 mg/dL, creatinine 1.5 mg/dL, lactate dehydrogenase enzyme 210 U/L, creatinine clearance 44.3 mL/min. Bone marrow biopsy and aspiration revealed that the bone marrow was infiltrated with blast cells of which 90 percent were nucleated cells. By morphologic and flow cytometric analysis revealing $CD13^+$ and $CD33^+$, the patient was diagnosed as having AML (FAB M1). The cytogenetic analysis of the patients revealed normal karyotype. Cytarabine (200 mg/m^2/d x 7) and mitoxantrone (10 mg/m^2/d x 3) were administered as a remission induction treatment. He received cytarabine (200 mg/m^2/d x 5) and idarubicine (12 mg/m^2/d for one day) for consolidation treatment after CR was achieved. Two months after the consolidation treatment, IL-2 was administered with a dose of 9 MU/day for a cycle of five consecutive days and a course of IL-2 was constituted by two cycles of IL-2 treatment. Fourth course of IL-2 treatment was started after 8^{th} month of his CR. On the 9^{th} day of the fourth course, a severe reaction occurred including hypotension which required pressor therapy, tachycardia, widespread erythema, eosinophilia, azotemia and respiratory distress. Because of all these side effects, we had to quit IL-2 treatment. Later IL-2 treatment was substituted with interferon-alfa 2a with 4.5 MU/2 days a week for 45 months. He has been alive and disease free for 71 months after his nephrectomy and 58 months after diagnosis for AML.

DISCUSSION

Patients with bilateral synchronous renal cell carcinoma have poor prognosis even surgery, conventional chemotherapy or radiotherapy were instituted[9]. IFN therapy has been reported to be effective in about 20% of advanced renal cell cancer[10]. IL-2 was used for the treatment of renal cell cancer and appears to possess encouraging anti-tumour activity. High doses of IL-2 with or without LAK cells led to successful results in about 30-35% of patients with 15-20% complete responses[3,7]. Figlin et al. analysed 203 IL-2 based treated patients with metastatic renal cell cancer. They reported that the overall median survival for all the patients was 18 months. Of these patients, 6% achieved complete response, 18% achieved partial response while 20% had proceeded with stable disease[8]. In the study of Negrier et al. 425 patients with metastatic renal cell carcinoma were randomly assigned to receive either IL-2, sc.interferon a2a (rIFN-a2a) or both. They reported that the response rates were 6.5%, 7.5% and 18.6%, and event free survival rates were 15%, 12% and 20%, respectively[11]. According to some studies, combination immunotherapy with IL-2 and IFN-a2a appear to be more effective than single agent[12]. Aggressive treatment of bilateral synchronous renal cell carcinoma is the only approach that can offer patients a life opportunity with a significant 5 years survival ranging between 60-77%[9]. In our patient a long complete remission achieved with nephron sparing surgery followed by immunomodulatory therapy consisting of IL-2 and IFN-a2a. Motzer et al. compared IFN-a2a and IL-2 combined therapy with monotherapy. They reported an increased toxicity with no improvement in survival[13].

Immunoactivating properties of IL-2 were observed in vitro and during IL-2 therapy in vivo. Nu-

merous studies demonstrated the fact that IL-2 potently activates NK-cell mediated cytotoxicity against several types of cultured and freshly recovered leukemia cells[4,14]. It has been shown that IL-2 is capable of generating cytotoxic T lymphocytes directed specifically against the tumour cells. Navo et al. analysed peripheral blood cells of cancer patients following IL-2 and they demonstrated a characteristic pattern of intense phagocytosis in granulocytes with respect to the base situation was present[15]. In addition Lauria et al. subjected that the sensitivity of AML blast to the lytic activity of NK cells correlates with event free survival[14]. In vitro and in vivo studies have been reported about the lytic effect of LAK cells on human leukemic blasts is present[4]. It has been reported that there is deficiency in natural killer and LAK cell function in leukemia patients whereas the patients with acute leukemia in complete remission may reveal satisfactory LAK activity[4,16]. In view of these findings, the feasibility of the use of IL-2 in patients with AML seems to be appropriate[17].

In this case we administered IL-2 in the first complete remission and achieved a remission for 58 months after diagnosis of AML. The studies with IL-2 therapy in the first remission are limited. Brune et al. evaluated 17 patients within the first complete remission. Twelve of them remained in CR with a median CR duration of 12 month's[18]. Cortes et al. reported a group of 18 patients treated with IL-2 in the first complete remission for whom the median CR duration was 12 months and 6 patients were in CR at a median follow-up of 64 months. Cortes et al. emphasize that use of IL-2 in first CR might be more beneficial, because the residual disease is minimum, and LAK activity and sensitivity of leukemia cells to LAK mediated cytotoxicity might be higher[19].

The most common dose limiting toxicities of IL-2 therapy are hypotension, weight gain, oliguria, respiratory insufficiency and neurotoxicity. Cytopenia coagulopathy and leukopenia are usually mild. As in our patient's therapy, these adverse effects sometimes may cause to withdraw IL-2. We continued the therapy with interferon-a2a which is another immunomodulatory agent particularly for RCC.

Most of the AML patients relapse, although they receive consolidation therapy containing high dose cytosine arabinoside or undergo allogeneic stem cell transplantation. In several randomised studies, the mean overall survival of the patients who were treated with standard therapy was only 9-15 months. Our patient received IL-2 followed IFN-2a for maintenance therapy and no relapse occured within a considerable time period. According to our opinion,the remission period of our patient was prolonged due to IL-2 therapy followed by IFN-a2a.

In patients who have two different malignancies such as in our patient, therapies known to be effective against both disease, i.e IL-2, should be considered. To our knowledge this is the first case who had both RCC and AML and achieved very long disease free and overall survival with convenient treatment including IL-2 and IFN-a2a maintenance.

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Adress for Correspondence:

Akýn UYSAL, MD

Department of Haematology-Oncology
Ýbn-i Sina Hospital, Ankara Medical School
Sýhhýye, Ankara, TURKEY

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