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# Non-cytotoxic CD4 Tumour-infiltrating Lymphocytes Induce Responses in Patients with Metastatic Renal Cell Carcinoma Previously Treated with Interleukin-2

**C. Mathiot, N. Thiounn, E. Tartour, T. Flam, C. Peyret, I. Joyeux, M. Zerbib, M. Brandely, B. Debré and W.H. Fridman**

WE PREVIOUSLY reported the lack of therapeutic effect of tumour-infiltrating lymphoytes (TIL) in patients with metastatic melanoma who have failed to respond to high-dose interleukin 2 (IL2) [1]. In order to test the ability of TIL to modify IL2 response in renal cell carcinoma (RCC), we treated, in a preliminary study, 6 patients. 4 patients had previously received high-dose IL2 and 2 had received a subcutaneous low dose. The characteristics of patients are summarised in Table 1, all were metastatic predominantly in lymph nodes and lung. Two types of response were observed: in 2 patients, who were partial responders to IL2 alone (patients 2 and 3), infusion of their TIL induced complete responses; in 2 other patients, whose tumour progressed after IL2 alone (patients 4 and 6), the infusion of TIL resulted in a stabilisation of the disease. These observations are in agreement with the theory proposed by Greenberg [2] of TIL efficacy when tumour burden is reduced. The second observation may also indicate that TIL may be efficacious without an IL2 effect, although this was only partial efficacy. The phenotype of these 4 patients was predominantly CD4, but with 30–40% of CD8-positive cells in 2 patients. More interestingly, the TIL exerted little or no cytotoxicity towards various targets, including autologous tumour (Table 1), whereas autologous cytotoxicity has been reported to be associated with response in melanoma [3]. This leads us to propose that other mechanisms, such as cytokine production by CD4+ T helper cells, are effective in RCC tumour control [4].

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*Table 1. Patients' characteristics*

| Patient | IL2 dose before TIL | Delay IL2 TIL (weeks) | Cells injected ($\times 10^{10}$) | Phenotype (%) CD3/ CD4/CD8/ CD56 | Cytotoxicity (E/T25/1) (%) K562/Raji/ autologous | Status after IL2 | Status 1 month after TIL | Status at 6 months | Status at 12 months |
|---|---|---|---|---|---|---|---|---|---|
| 1 | $48\times10^6/m^2/w\times5w$ | 5 | 3.7 | 99/8/91/1 | 1/9/14 | PD | PD | Dead | Dead |
| 2 | $48\times10^6/m^2/w\times5w$ | 5 | 7.6 | 88/64/37/1 | 16/10/1 | PR | CR | CR | CR |
| 3 | $48\times10^6/m^2/w\times5w$ | 6 | 0.23 | 95/65/29/27 | 23/4/0 | SD | PR | CR | CR |
| 4 | $48\times10^6/m^2/w\times5w$ | 10 | 0.56 | 90/89/4/7 | 4.6/2/13 | PD | SD | SD | SD |
| 5 | $9\times10^6/d\times5w$ | 10 | 0.02 | 85/83/5/22 | 25/10/10 | PD | SD | Dead | Dead |
| 6 | $9\times10^6/d\times5w$ | 8 | 1.1 | 90/65/41/19 | 7/2/0 | PD | SD | SD | NE |

PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response; NE, non-evaluable; d, day; w, weeks; IL2, interleukin-2; TIL, tumour-infiltrating lymphocytes.


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# Feasibility and Compliance of Epirubicin Plus Ambulatory Continuous Infusion Ifosfamide at Escalating Doses in Advanced Soft Tissue Sarcomas: a Phase I Study

**R. Palumbo and S. Toma**

ANTHRACYCLINES (doxorubicin or epirubicin) plus ifosfamide is the most widely used and effective combination in advanced and/or metastatic soft tissue sarcomas (STS). In determining the ideal combination of the two drugs, consideration has to be given to their specific toxicities, the need to use the maximum tolerable dose, and the dose–response relationship for anthracyclines [1–4]; and, more recently, for ifosfamide [5, 6]. The use of continuous infusion (CI) has been confirmed as a valid option to avoid renal and neurological side effects, which appear to be the dose-limiting factors when high doses of ifosfamide are given [7–10]. Ambulatory CI has been shown to be feasible for patients with advanced, pre-treated disease, with good patient compliance [10].

In view of the above, we conducted a phase I–II study to define the maximum tolerated dose (MTD) of ifosfamide when given in association with a fixed dose of epirubicin, and the dose-limiting toxicities of the combination with at least two cycles of therapy, in a day-hospital regimen.

From December 1993 to July 1994, 17 adult patients with histologically confirmed advanced STS were studied. Epirubicin was given at a fixed dose of 110 mg/m$^2$/course (55 mg/m$^2$, intravenously bolus, days 1 and 2) combined with ifosfamide administered by CI over 4 consecutive days, through a portable infusion pump connected to a subcutaneous port system. Total ifosfamide dose/course was escalated by 1 g/m$^2$, starting from 9 g/m$^2$/course, in cohorts of 3–5 patients until the MTD of the combination was determined. Equidose mesna uroprotection (by CI, days 1–5), and granulocyte-colony stimulating factor support (200 $\mu$g/m$^2$/day, subcutaneously, days 6–13) were provided in all patients; courses were repeated every 3 weeks. Toxicity was strictly monitored, as previously described [4, 10].

If 2 or more patients at any dose level developed grade 3 non-haematological or grade 4 haematological toxicity requiring treatment delay, or if 2 of the 3–5 patients did not complete the planned two courses of treatment due to poor compliance, the immediately preceding ifosfamide dose level was considered the MTD of the combination.

All patients completed the planned two courses of treatment; 2 patients received a third cycle and one had four courses. The toxicities observed during the total 37 courses are summarised for ifosfamide dose level in Table 1. No toxic death occurred and no patient required hospitalisation for treatment-related side effects.

At the 11 g/m$^2$ ifosfamide dose level, haematological toxicity precluded further dose escalation, with 5/5 patients developing grade 4 leucopenia, that required a treatment delay of 1–2 weeks and transfusion support.

In combination with epirubicin at the fixed dose of 110 mg/m$^2$, ifosfamide at 10 g/m$^2$ by CI with mesna uroprotection was identified as the MTD. At this dose level, haematological

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