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Chemoimmunotherapy of Metastatic Malignant Melanoma
The Salpétrière Hospital (SOMPS) Experience

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Optimistic results were obtained in the treatment of 39 patients with surgically incurable metastatic malignant melanoma using a regimen including 2 to 3 monthly induction cycles of *cis*-diamminedichloroplatinum (CDDP), recombinant interleukin-2 (rIL-2) and interferonα-2a (IFNα-2a). 33 of 39 patients were pretreated with chemotherapy (dacarbazine and/or fotemustine:31, CDDP:6) and 17 of 39 with IFNα-2a. Overall response rate was 54% with 13% achieving a complete response for up to 59+ weeks. Moderate to severe side-effects were reversible on rIL-2 cessation and toxicity was manageable in a routine inpatient setting. These results are especially encouraging as they were seen in previously treated patients, classically low responders, including 3 who were resistant to cisplatin or other platinum complexes. The question remains if this regimen bypasses traditional mechanisms of drug resistance.
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INTRODUCTION

INTERLEUKIN-2 (IL-2) has a far reaching impact on cells of the immune system and on the ability of the tumour-bearing host to resist neoplastic disease [1]. Through expansion of cytolytic T-cell clones, IL-2 augments cellular immunity to tumour-associated antigens [2]. Through induction of γ-interferon, IL-2 enhances the anti-tumour effects of macrophages [3]. Through activation of a subpopulation of mononuclear cells with non-histocompatibility leukocyte antigen (HLA) restricted cytotoxic potential, IL-2 can induce additional cellular reactivity against tumour target cells [4–6]. Together, these IL-2-mediated immunological effects may play an important role in controlling the growth of transformed cells.

After it had been demonstrated in animal models that recombinant IL-2 (rIL-2) and rIL-2-activated mononuclear cells can exhibit antineoplastic effects against metastatic cancer [4–6], clinical trials with rIL-2, with or without *in vitro* activated cells [lymphokine-activated killer (LAK) or tumour infiltrating lymphocytes (TIL)] have confirmed the anti-tumour potential of the rIL-2 therapy [7–16].

The first clinical studies using the intravenous (i.v.) bolus schedule of high-dose rIL-2 reported severe life-threatening toxicities. Since then a large number of studies have been undertaken in an attempt to diminish these toxicities [9–13, 17].

Evidence suggests that continuous presence of rIL-2 is mandatory for its mode of action and this is best achieved by continuous infusion [14].

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Recently, European multicentre trials [15–18] have confirmed that continuous infusion can be safely given outside the intensive care unit (ICU) setting. Antitumour efficacy has been confirmed for renal cancer, melanoma and colorectal cancer (the latter tumour types in combination with sequential chemotherapy).

There are several reasons to consider sequential chemotherapy in the design of rIL-2/chemotherapy studies in melanoma; biological therapy with rIL-2 may result in improved blood supply to tumour cells and there may also be synergy between chemotherapy and biological therapy in terms of anti-tumour effect.

The combination rIL-2/dacarbazine (DTIC) in melanoma gives a response rate in the order of 10–25% [16, 19, 20]. The sequencing and timing of the chemotherapy and immunotherapy may be a determining factor for efficacy and the response rate might be improved by optimising the treatment schedules in future trials.

In addition, based on recent experience, the combination of cisplatin-containing chemotherapy and immunotherapy seems a very interesting therapeutic option. While cisplatin at doses ≤ 100 mg/m^2 produces response rates of less than 15% when used as a single agent [21], its combination with rIL-2 and interferon alfa (IFN-α) has been shown to be very effective. The combination of cisplatin with bolus rIL-2 has been reported to induce a response rate of 37% [22], whereas a study of combined cisplatin and DTIC chemotherapy alternated with low-dose bolus rIL-2 and IFN-α immunotherapy was shown to induce a 43% response rate [23]. In an ongoing study, cisplatin and DTIC chemotherapy was alternated with rIL-2, given by continuous i.v. infusion (CIV), and IFN-α immunotherapy. At interim analysis the response rate was 56% [24]. Other studies have also suggested an advantage for the combination of chemotherapy and IL-2–IFN in metastatic malignant melanoma [25, 26].

Sequential rather than simultaneous chemoimmunotherapy is proposed to permit at least partial separation of toxicities and to avoid any negative impact of simultaneous cytotoxic drug on the

lymphoproliferative response to rIL-2. The toxicity profile experienced on these pilot studies of combination chemo/immunotherapy was as expected for these drugs and consisted mainly of fever, chills, hypotension, cutaneous toxicity, haematological and gastrointestinal toxicity. However, the toxicity was grade II/III at maximum and has been shown to be manageable in a non-ICU care unit.

THE SALPÉTRIÈRE EXPERIENCE

Similarly, our experience at the Salpétrière Hospital in Paris with chemoimmunotherapy regimens in metastatic malignant melanoma seems very promising and we report here the high response rate and long-term remissions of metastatic malignant melanoma treated by *cis*-diamminedichloroplatinum (CDDP)–rIL-2–IFN-α.

Since December 1990, 39 patients (21 men/18 women) with metastatic malignant melanoma have been treated with two to three monthly induction cycles of chemoimmunotherapy combination: CDDP 100 mg/m^2 on day 1, rIL2 18 × 10^6 U/m^2/day by 24-h i.v. infusion on days 3 to 6 and 17 to 21, and simultaneous subcutaneous IFNα-2a 9 × 10^6 U three times weekly. Response was assessed after completion of two cycles and then monthly. 33 of 39 patients were pretreated with chemotherapy (85%) (dacarbazine and/or fotemustine: 31, CDDP: 6) and 17 of 39 with IFNα-2a (44%). Median age was 44 years (range 21–68) and median ECOG performance status was 0 (range 0–2). Sites of metastatic disease included lymph nodes: 25, skin/soft tissue: 22, lung: 17, liver: 8, bone: 5 and others: 11. All patients received the two induction cycles and were fully evaluable.

Overall response rate was 54% [95% confidence interval (CI): 38–70] with 5 of 39 patients achieving a complete response (13%) for 59+, 43+, 42+, 15 and 13 weeks and 16 of 39 (41%) a partial response for 46+, 35+, 31, 28, 24, 22, 21, 18+, 18, 16, 15, 14+, 13+, 12 and 9+ weeks.

Responding sites included lymph nodes: 17, soft tissue: 10, lung: 8, liver: 3, bone: 1 and others: 5. The median survival is 47 weeks (range 7–63+). At present 16 patients have died including 7 patients with metastases to the CNS as the main site of progressive disease.

Fever, chills, nausea and vomiting, diarrhoea and cutaneous toxicity were observed in most patients, being moderate to severe (grades II–III) in intensity but manageable and reversible on rIL-2 cessation. All patients experienced hypotension including 17 grade III–IV well controlled with low dose of dopamine. Renal toxicity was fully reversible. Haematological toxicity consisted of anaemia grade III–IV: 15, leucopenia grade III–IV: 14 and thrombocytopenia grade III–IV: 10. No life-threatening toxicity was observed, but 24-h medical nursing/surveillance was the rule during rIL-2. Thus CDDP combined with rIL-2 and IFNα-2a allows us to achieve a 54% response rate (RR) (95% CI: 38–70) including 13% of complete response with a median duration of 24 weeks. A clear cut survival benefit is obtained for responding patients (median survival not reached at 48 weeks) compared to non-responders (median survival: 28 weeks) (P = 0.001, Fig. 1). The toxicity was manageable (no life-threatening toxicity, no toxic death) with treatment given in an inpatient non-ICU setting. Given dose intensity/planned dose intensity according to Hryniuk method [27] was CDDP 0.89 (0.66–1.00), rIL2 0.84 (0.53–1.00), IFNα-2a 0.47 (0.08–0.94).

DISCUSSION

With a 54% overall response rate including 13% complete responses, the results reported here are very encouraging.

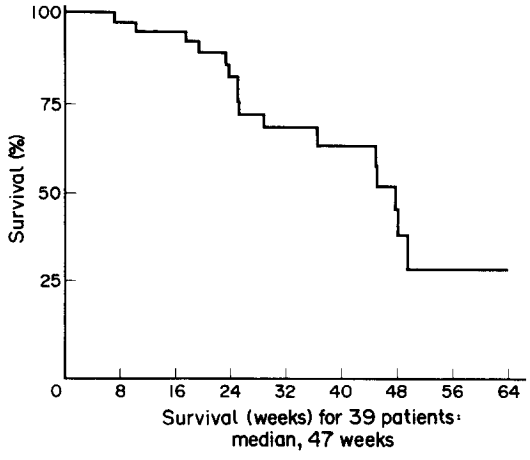

Fig. 1.

Although the response rate of both complete and partial responders can be compared favourably with other recently published series of chemoimmunotherapy including rIL-2, these are the only results that may demonstrate true synergy among these three drugs because of the use of standard-dose cisplatin as the single chemotherapeutic agent. Indeed, as shown in Table 1, most of the related studies reported to date have used either high-dose cisplatin with WR 2721 as a protective agent [22] or standard-dose cisplatin combined with one (DTIC) [23, 24], two (vinblastine–DTIC) [25] or three other drugs [tamoxifen, DTIC and 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU)] [26].

Moreover, the high response rate which was obtained occurred in previously treated patients, including 3 who were resistant to cisplatin or other platinum complexes (carboplatinum, oxalloplatinum). This point is very important since it is known in melanoma, as well as in most other solid tumours, that pretreated patients usually have a significantly lower response rate than chemotherapy-naive patients suggesting, therefore, that this regimen may bypass or reverse traditional mechanisms of drug resistance.

Responses were seen in visceral sites including lung, liver and bone (48%) as well as in non-visceral sites (52%). However, response seems significantly correlated to the extent of the disease. The response rate dropped from 70% in patients with ≤2 involved sites to 20% in patients with ≥3 sites (P = 0.007). An advantage was also seen for patients demonstrating vitiligo during treatment.

There is no obvious benefit of maintenance therapy in our results. Indeed, among the 16 patients who entered maintenance treatments, 13 had relapses within an average of 3 months from the time of entry into maintenance. This may be due to the lack of efficacy of subcutaneous low-dose of IL-2 in metastatic malignant melanoma.

The toxicity of this chemoimmunotherapy combination was manageable with treatment being given in a routine inpatient setting. Twenty-four-hour medical and nursing surveillance was the rule during IL-2–IFNα-2a treatment, but no life-threatening toxicity was observed and an ICU was not required. Severe fatigue, chills and weight loss were very frequent but were rarely limiting. Haematological toxicity was significant, but of short duration and most often caused no morbidity. Other toxicity, in particular, renal toxicity, was fully reversible on IL-2 cessation. The feasibility of this regimen is partly demonstrated by the fact that we administered more than 70% of the scheduled dose

Table 1. *Sequential CDDP/rIL-2-containing regimens*

Study	Chemotherapy	Immunotherapy	No. evaluable	CR (%)	PR (%)	RR (%)
Demchak [23]	CDDP high doses	rIL-2: high doses bolus	27	3 (11)	7 (26)	10 (37)
Hamblin [25]	CDDP + DTIC	rIL-2 + IFNα	12	3 (25)	7 (58)	10 (83)
Blair [24]	CDDP + DTIC	rIL-2 (outpatient)	28	5 (18)	7 (25)	12 (43)
Legha [26]	CDDP + VLB + DTIC	rIL-2 + IFNα	30	6 (20)	11 (36)	17 (56)
Richards [27]	CDDP + BCNU + DTIC + TMX	rIL-2 + IFNα	42	10 (24)	14 (33)	24 (57)
Present study	CDDP	rIL-2 + IFNα	39	5 (13)	16 (41)	21 (54)

CR, complete response; PR, partial response; RR, response rate.

intensity of CDDP and IL-2 according to the Hryniuk method [27].

The only reported information regarding the clinical or biological toxicities of other IL2-containing chemoimmunotherapy protocols are those of Legha *et al.* using the triple chemotherapy regimen CDDP/DTIC vinblastine (VLB) combined with rIL2–IFNα-2a [25]. Our regimen logically appears much less toxic as they reported grade III or IV neutropenia and thrombocytopenia in 96% and 90%, respectively. Moreover the myelosuppression in Legha's series was complicated by septic episodes in 19 out of the 30 evaluated patients and the need for platelet transfusions in 14 patients.

Although promising, because of their interesting efficacy/toxicity ratio, and in view of the fact that neither IL-2 nor IFNα-2a given as monotherapy [28] or bitherapy [29, 30] has shown equivalent efficacy, our results need to be confirmed in a larger scale study. Furthermore, several important questions remain to be answered: what is the role of rIL-2 in these results? Are there ways to increase the complete response rate? Are there ways to prevent relapse in the central nervous system? While pilot studies with different maintenance treatments or combined tamoxifen or nitrosourea help in addressing some of these questions, a larger multicentre study is to be started in the very near future comparing rIL-2–CDDP–IFNα-2a to CDDP–IFNα-2a that may definitely indicate the value of rIL-2 in combination chemoimmunotherapy for metastatic malignant melanoma.

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