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# Letters

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## Interferon-α–Carboplatin Combination Therapy for Metastatic Melanoma: Phase II Study

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IN PATIENTS with unresectable metastatic melanoma, treatment with mono-/combination therapy is still considered unsatisfactory [1]. With recombinant cytokines such as interferon-α (IFN-α) and interleukin-2 (IL-2), used alone or in combination with lymphokine-activated killer cells, response rates between 20 and 30% have been achieved in far advanced stages of the disease [2, 3]. Currently, a therapeutic strategy is to combine chemotherapy with one or both of these cytokines, particularly IFN-α, in order to investigate a possible additive or synergistic effect of both these treatments having diverse mechanisms of action. From preclinical experiments there is evidence that cisplatin and IFN have synergistic antitumoral activity *in vitro* [3]. Furthermore, in clinical studies performed with this combination, objective response rates of approximately 25% have been documented for metastatic melanoma [4, 5]. However, in one of these studies, combination therapy was accompanied by a higher incidence of a haematological and renal toxicity [5]. Therefore, we evaluated the possible therapeutic efficacy of the second generation of platinum compounds, i.e. carboplatin — lacking nephrotoxicity — in combination with IFN-α-2b for treatment of metastatic melanoma.

Patients with unresectable metastatic melanoma, presenting with progressive disease and with a least one measurable lesion, were eligible for this phase II study. Other inclusion criteria were a performance status > 60% (Karnofsky), life expectancy > 3 months and adequate bone marrow, hepatic and renal functions. Patients with previous IFN therapy as well as those presenting with brain metastases were ineligible. Prior to entry, all patients were required to give informed consent. The protocol was approved by the ethical committee of the Faculty of Medicine (Vienna University, Austria).

Treatment performed on an outpatient basis was as follows: 3 million U/m$^2$ IFN-α-2b (IntronA, AESCA Austria) three times a week, subcutaneously on days 1–5 and on day 8 carboplatin (Myers Squibb, Austria) 400 mg/m$^2$ was given by intravenous bolus infusion. On day 15, this was followed by IFN-α-2b 3 million/m$^2$ three times a week up to day 27. Cycles were repeated every 28 days.

19 consecutive patients [10 male, 9 female, mean age 56 years (range 34–70) have been included in this study between January 1989 and February 1991. 6 patients (32%) had previous therapy (DTIC 1, BCNU 4, radiotherapy 1). Mean Karnofsky scale was 90% (range 60–100%). Single, metastatic sites included the lung for 5 patients, lymph nodes for 1 patient. 10 patients had metastatic involvement at two sites, 2 patients in three sites, and 1 patient had multimetastatic lesions, of these 7 had liver metastases.

All patients included were evaluable for toxicity and response criteria (WHO) [6]. Patients received a total number of 175 cycles (median duration more than 9 months). 8 of 19 patients (42%) showed objective responses (95% confidence interval 21.1–66.0%), i.e. 5 complete remissions (CR) (26%), 3 partial remissions (PR) (16%). 7 patients had stable disease (37%), whereas 4 (21%) had disease progression. Median duration of response was 19 months for CR (59$^+$, 46$^+$, 19, 12, 11 months) and 9 months for PR (11, 9, 6 months, median 11 months). Median duration of stable disease was 6 months (13, 8, 8, 6, 5, 5, 4).

Responding sites included 6 in the lung (which was in 3 patients the only metastatic site). Of the patients with CR, 4 had a response in the lung, 1 in the liver, 2 in lymph nodes, and 2 in skin metastases. Of patients with a PR, 2 had a response in the lung and 2 in the liver. Life table analysis according to Kaplan–Meier gives an overall median survival time of 11 months (range 2–54$^+$ m) with survival probability of 19 months for 25% of the patients.

Toxicity was graded according to WHO scale. No nephrotoxicity was observed, haematological toxicity (leucopenia), grade 2, was present in 52%, grade 3 in 10% and grade 4 in 5% of patients. Gastrointestinal toxicity, grade 2, was observed in 32% and grade 3 in 10% of the patients. Flu-like symptoms, grade 2, appeared in approximately 10% of patients. In 36/175 cycles of carboplatin and 34/175 cycles of IFN, doses had to be reduced by 25% due to side-effects. A toxicity-related interruption of therapy was required in 1 patient (grade 4 leucopenia).

While this study was in progress, results of several phase II/III studies, that had broken the critical point for response rates, i.e. 30–35% using IFN and/ or IL-2 together with single or combination chemotherapy, were presented [7–9], thus suggesting synergistic activity of these agents. Although promising because of the improved efficacy/toxicity ratio, these studies — including our own — have to be confirmed on a larger scale. An ongoing Austrian multicentre study, using the IFN-α–CDDP combination regimen of the presented phase II study, has so far given remission rates of approximately 40%. A further, randomised prospective study is required to confirm the therapeutic benefit of the combination therapy as used in this study.

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1. Parkinson DR, Veronesi U, Kirkwood JM. Malignant melanoma. Educational book. *Am Soc Clin Oncol* 1993, 84–94.
2. Kirkwood JM, Ernstoff MS. Role of interferons in the therapy of melanoma. *J Invest Dermatol* 1990, **95**, 180–184.
3. Wadler S, Schwartz EL. Antineoplastic activity of the combination of interferon and cytotoxic agents against experimental and human malignancies. A review. *Cancer Res* 1990, **50**, 3473–3486.

4. Margolin KA, Doroshow JH, Akman SA, *et al.* Phase II trial of cisplatin and α-interferon in advanced malignant melanoma. *J Clin Oncol* 1992, **10**, 1574–1578.
5. Richner J, Cerny T, Micksche M, Brunner W. Phase II study of continuous subcutaneous alpha 2b interferon (IFN) combined with cisplatin (CDDP) in advanced malignant melanoma (MM) *Proc Am Soc Clin Oncol* 1990, **9**, 280.
6. WHO. *Handbook for Reporting Results of Cancer Treatment.* Geneva, Offset Publication. World Health Organization No. 48, 1979.
7. Falkson CI, Falkson G, Falkson C. Improved results with the addition of interferon alfa-2b to dacarbazine in the treatment of patients with metastatic malignant melanoma. *J Clin Oncol* 1991, **9**, 1430–1408.
8. Khayat D, Borel C, Tourani JM, *et al.* Sequential chemiommunotherapy with cisplatin interleukin-2, and interferon alfa-2a for metastatic melanoma. *J Clin Oncol* 1993, **11**, 2173–2180.
9. Pyrhöhen S, Hahka-Kemppinen M, Muhonen T. A promising interferon plus four-drug chemotherapy regimen for metastatic melanoma. *J Clin Oncol* 1992, **10**, 1019–1026.

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# Lymphomas Associated with the Endemic (African) Variant of Kaposi's Sarcoma: A Chemosensitive but Fatal Entity

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THERE ARE very few reports of the association between the endemic (African), non-AIDS-related variant (AKS) of Kaposi's sarcoma (KS) and secondary lymphoma compared with reports on classic KS [1–3]. The scarcity of reported cases may be related to under-reporting, due to the acute lack of medical facilities in Africa and a lack of adequate follow-up, as well as to increased morbidity through exacerbation of infectious diseases.

Between 1981 and 1992, 47 HIV-negative Black males were referred to the Johannesburg General Hospital for treatment of their KS. The majority (37/47, 79%) presented with skin disease, and 10/47 (21%) patients had additional gastrointestinal tract, lymph node and lung involvement. Staging and treatment modalities (mainly radiotherapy) have been described previously [4].

2 patients with KS limited to the skin (stage I), which regressed almost totally with 'involved field' radiotherapy (24 Gy), presented simultaneously with generalised lymphadenopathy (peripheral, mediastinal and para-aortic). Meticulous multiple lymph node biopsies revealed follicular lymphoma and peripheral T-cell lymphoma, respectively. Both received COPP (cyclophosphamide, oncovine, procarbazine, prednisone) regimen with a marked response, albeit of short duration (both patients subsequently died).

A third patient with stage IV KS presented with advanced lymphadenopathy due to immunoblastic lymphoma. Both his diseases responded initially to vinblastine/etoposide (plus radiotherapy) and later to a CHOP (cyclophosphamide, doxorubicin, oncovine, prednisone) regimen, but he relapsed 3 months later and died.

The fourth patient presented with advanced KS (skin, peripheral lymph nodes), as well as hepatomegaly, ascites and pleural effusion. Bone marow trephine biopsy demonstrated infiltration with a large cell lymphoma of B-cell origin. Immune function tests showed an absolute T-cell lymphopenia with a low $T_4/T_3$ ratio (0.78 : 1). Following cytarabine/interferon-α therapy, a significant response was achieved. The patient was then continued on CHOP with a continued response. 4 months after completion of his chemotherapy, he relapsed with massive hepatosplenomegaly and pancytopenia due to extensive lymphomatous infiltration of the bone marrow.

Data concerning AKS-related lymphomas are very rare and are mentioned only sporadically in the literature. All the reported cases lack proper staging, treatment, assessment of response and sufficient follow-up [5].

Recent reports have demonstrated a moderate alteration in cell-mediated immunity in AKS [6]. Protein malnutrition, chronic infections (e.g., hepatitis), tropical infections (e.g., malaria) and the wide use of alkylating agents may contribute to impaired cell immunity. The compromised immunity may lead to T-cell regulatory dysfunction and unopposed proliferation of abnormal B-cells, emerging in malignant lymphomas [7]. Other authors postulate a common pathogenetic mechanism between KS and lymphoma [8].

Another hypothesis is that certain antigenic stimuli may result in the simultaneous proliferation of both lymphoid and endothelial cells which, in the presence of immune dysfunction, may result in the simultaneous appearance of KS and lymphoma.

In conclusion, the improved outcome of patients with AKS due to modern therapeutic methods may unmask an increased number of chemoresponsive but biologically aggressive lymphomas.

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1. Stein ME, Kantor A, Spencer D, Bezwoda WR. Classical Kaposi's sarcoma in Caucasians in Africa — experience at the Johannesburg Hospital (1978–1992). *Dermatology* 1994, **188**, 182–187.
2. Piette WW. The incidence of second malignancies in subsets of Kaposi's sarcoma. *J Am Acad Dermatol* 1987, **16**, 855–861.
3. Lothe F, Murray JF. Second primary neoplasms associated with Kaposi's sarcoma in African patients — an autopsy report. *Acta Clin Int Cancer* 1962, **18**, 100–116.
4. Stein ME, Lakier R, Kuten A, Spencer D, Ruff P, Bezwoda WR. Radiation therapy in endemic (African) Kaposi's sarcoma. *Int J Rad Oncol Biol Phys* 1993, **27**, 1181–1184.
5. Safai B. Kaposi's sarcoma: a review of the classical and epidemic forms. *Am NY Acad Sci* 1982, **437**, 373–382.
6. Lulat AGM. African Kaposi's sarcoma. *Trans R Soc Trop Med Hyg* 1989, **83**, 2–4.
7. Mairing C, Fiorini R, Bonechi B, Malatti E, Brambilla L. Immunologic and immunogenetic features of primary Kaposi's sarcoma. *Cancer* 1985, **55**, 1899–1901.
8. Safai B, Mike V, Giraldo G, Beth E, Good RA. Association of Kaposi's sarcoma with second primary malignancies: possible etiopathogenic implications. *Cancer* 1980, **45**, 1472–1479.

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