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# Malignant Melanoma Treated with Natural Interferons Alfa and Beta and DAV

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A 60-YEAR-OLD man was referred to our department in July 1986. Examination showed a large macular lentiginous melanoma, measuring 1.5 × 1.2 cm, on the sole of his left foot. The tumour was excised surgically on 15 August. Light microscopy revealed level V (pT4) invasion by neoplastic cells. Accordingly, the patient was diagnosed as being at stage III (pT4a, N0, M0). Systemic chemotherapy (dacarbazine/nimustine/vincristine) DAV [1] was given until August 1986. The patient maintained complete remission for about 4 months until December. He then noticed metastatic tumours on the left thigh and in the inguinal region. Natural interferon alfa (IFN-α) was administered, surgical excision was done and systemic DAV was given until March 1987. Natural IFN was subcutaneously injected. IFN-β 3μU was given twice a month for maintenance. The patient has since maintained complete remission for about 5 years from February 1987.

Before IFN-α therapy, only a small number of infiltrating cells were detected in the lesion with a series of monoclonal antibodies and hetero-antisera. After this treatment, the infiltrating cells increased. Demarcated T-cell and B-cell regions were evident around the clusters of neoplastic cells.

The 5-year survival of patients with stage III malignant melanoma excluding N2 treated with DAV plus IFN-β is better than that of patients treated with BCG plus DAV, picibanil (OK432) plus DAV, DAV alone or dacarbazine alone. The 5-year survival of patients treated with IFN-β plus DAV or dacarbazine was 84%, whereas that of patients treated with BCG plus DAV or dacarbazine, and picibanil plus DAV or dacarbazine was 58 and 56%, respectively.

Recently, biological response modifiers (BRMs) have been used therapeutically against malignant neoplasms [2–4], but their effect is not sufficient to cure. Although an increased number of tumour infiltrating cells are seen in the lesion after local injection of BRMs, such as IFN-α, IFN-β, IFN-γ or tumour necrosis factor alpha, these changes are not significant. BRMs may exert an immunopotentiating effect via the immune system of the patient in addition to direct toxicity against tumour cells [4–6]. Combination therapy with BRMs and chemotherapeutic agents has been used in patients with advanced malignancy [3,8–10]. Combination therapy with IFN-β plus DAV is one such treatment. Our experience with this combination did not demonstrate a significant advantage compared with other types of therapy for stage III malignant melanoma.

1. Ishihara K, Ikegawa S. Diagnosis and treatment of malignant melanoma. *Gan To Kagaku Ryoho* 1985, **12**, 1727–1734.
2. Mülle JJ, Yang J, Shu S, Rosenberg SA. The anti-tumor efficacy of lymphokine-activated killer cells and recombinant interleukin 2 *in vivo*: direct correlation between reduction of established metastases and cytolytic activity of lymphokine-activated killer cells. *J Immunol* 1986, **136**, 3899–3909.
3. Munker R, Koeffler P. *In vitro* activation of tumor necrosis factor on myeloid leukemia cells. *Blood* 1987, **69**, 1102–1108.
4. Stadler R, Mayer-da-Silva A, Bratzke B, Garbe C and Orfanos C. Interferons in dermatology. *J Am Acad Dermatol* 1989, **20**, 650–656.
5. Taguchi T, Abe S, Nakano K, Matsui Y, Sohmura Y. Synergistic enhancement of the antitumor activity of recombinant human TNF-alpha by recombinant human IFN-gamma. *Cancer Detect Prev* 1988, **12**, 1–6.
6. Adler A, Chervenick PA, Whiteside TL, Lotzova E, Herberman RB. Interleukin 2 induction of lymphokine-activated killer (LAK) activity in the peripheral blood and bone marrow of acute leukemia patients. I. Feasbility of LAK generation in adult patients with active disease and in remission. *Blood* 1988, **71**, 709–716.
7. Peace DJ, Cheever MA. Toxicity and therapeutic efficacy of high-dose interleukin 2. *In vitro* infusion of antibody to NK-1.1 attenuates toxicity without compromising efficacy against murine leukemia. *J Exp Med* 1989, **169**, 161–173.
8. Stadler R, and Garbe C. Disseminated malignant melanoma. New therapeutic approaches. *Int J Dermatol* 1991, **30**, 239–242.
9. Miller RL, Steis RG, Clark JW, *et al.* Randomized trial of recombinant alpha 2b-interferon with or without indomethacin in patients with metastatic malignant melanoma. *Cancer Res* 1989, **49**, 1871–1976.
10. Falkson CI, Falkson G, Falkson HC. Improved results with the addition of interferon alfa-2b to dacarbazine in the treatment of patients with metastatic malignant melanoma. *J Clin Oncol* 1991, **19**, 1403–1408.

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# Multiple Myeloma in Two Sisters

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FAMILIAL OCCURRENCE suggests a role for genetic factors in the pathogenesis of multiple myeloma. We describe multiple myeloma in two sisters. Case 1 (52, admitted in December 1989 because of osteolytic lesions in ribs and spine); when first seen she was confused and dehydrated with chest and back pain.

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*Table 1. Laboratory data*

| | Case 1 | Case 2 |
|---|---|---|
| Monoclonal protein | IgG-lambda | IgG-lambda |
| Serum M-component (g/l) | 69.70 | 3.15 |
| Marrow plasma cells (%) | 70 | 33.5 |
| Lytic lesions | + | − |
| IgA (g/l) | 1.32 | 0.17 |
| IgM (g/l) | 0.77 | 0.06 |
| Serum calcium (mmol/l) | 3.64 | 2.25 |
| Serum creatinine (μmol/l) | 458 | 60 |
| Haemoglobin (g/dl) | 8.2 | 11.4 |

Multiple myeloma IgG lambda stage IIIB was diagnosed. Laboratory indices are listed in Table 1. She was treated with intravenous fluids and haemodialysis, with partial reversion of renal failure. She also received melphalan and prednisolone and later M2 (vincristine, melphalan, cyclophosphamide, benu and prednisolone) but she died from disease progression in December 1990. Case 2 (46, referred in April 1978 because of a gamma monoclonal spike during serum electrophoresis); she was symptom-free. There was no anaemia, azotaemia or bone lesions, or Bence-Jones proteins in a urine specimen. IgG lambda was 28.30 g/l. The bone marrow aspirate contained 22% plasma cells. She soon abandoned follow-up but returned in March 1990 still symptom-free. Multiple myeloma IgG lambda stage IA was diagnosed (Table 1).

Since 1954 [1], multiple myeloma in two or even three [2] first-degree members of the same family has been reported, [3, 4]. There is a higher frequency of other immunoglobulin abnormalities in relatives of such patients such as monoclonal gammopathy of unknown significance and Waldenstrom macroglobulinaemia [5, 6]. However, cases in spouses [7, 8], including cases of successive spouses of the same person [9] and clusters of cases [10], raise the possibility of a role for environmental factors in the pathogenesis of multiple myeloma. Environmental factors acting on genetically predisposed people may produce the condition.


1. Mandema E, Wildervanck LS. La maladie de Kahler (meylomes multiples) chez deux soeurs. *J Genet Hum* 1954, **3**, 170–175.
2. Horwitz LJ, Levy RN, Rosner F. Multiple myeloma in three siblings. *Arch Intern Med* 1985, **145**, 1449–1450.
3. Shoenfeld Y, Berliner S, Shaklai M, Gallant LA, Pinkhas J. Familial multiple myeloma. A review of thirty-seven families. *Postgrad Med J* 1982, **58**, 12–16.
4. Bourguet CC, Grufferman S, Delzell E, DeLong E, Cohen H. Multiple myeloma and family history of cancer. *Cancer* 1985, **56**, 2133–2139.
5. Zawadzki ZA, Aizawa Y, Kraj MA, Haradin AR, Fisher B. Familial immunopathies. *Cancer* 1977, **40**, 2094–2101.
6. Youinou P, Goff P, Saleun JP, *et al.* Familial occurrence of monoclonal gammapathies. *Biomedicine* 1978, **28**, 226–232.
7. Kanoh T. Multiple myeloma in spouses. *Eur J Haematol* 1988, **41**, 397.
8. Pietruszka M, Rabin BS, Srodes C. Multiple myeloma in husband and wife. *Lancet* 1976, **i**, 314.
9. Kyle RA, Greipp PR. Multiple myeloma: houses and spouses. *Cancer* 1983, **51**, 735–739.
10. Kyle RA, Herber L, Evatt BL, Heath CW. Multiple myeloma: a community cluster. *JAMA* 1970, **213**, 1339–1341.