*Table 1. CSF methotrexate concentrations ($\times 10^{-6}$ mol/l)*

| Days after treatment | First dose (5 mg) | Second dose (5 mg) |
|---|---|---|
| 1 | 41.3 | — |
| 2 | — | 1.86 |
| 3 | 3.2 | — |
| 6 | 0.18 | — |
| 7 | — | 0.57 |
| 8 | — | 0.09 |
| 14 | — | 0.02 |
| 21 | — | 0.01 |

cytology and computerised tomography of the cerebrum were normal. After 21 days, the patient recovered from neurotoxicity.

Analysis of the data revealed a methotrexate half-life in the CSF of approximately 15 h (Table 1). Previous studies of intrathecal methotrexate treatment in patients aged up to 40 years found: (i) the half-life of methotrexate in the CSF is longer in adolescents and adults compared with children [3]; (ii) variations in methotrexate CSF concentrations can be decreased in patients aged between 3 and 40 years if they receive a constant intrathecal dose, rather than a dose adjusted for body surface area [3]; (iii) dose adjustments according to body surface area are recommended in children below 3 years [3]; (iv) the mean half-life of methotrexate is approximately 4.5 h [4]; (v) the disappearance rate is independent of the applied dose [4]; and (vi) in patients showing acute onset of neurotoxic symptoms, methotrexate CSF concentrations measured after 48 h exceed $0.2 \times 10^{-6}$ mol/l [4, 5]. In practice, intrathecal methotrexate can safely be administered in patients up to 40 years of age, when the methotrexate CSF concentration is below this level.

Our case resembles the transient neurological disorder reported after high-dose intravenous methotrexate infusion [2], and is probably due to prolonged exposure of the cerebrum to methotrexate concentrations above the critical level. However, the dose of 5 mg is low compared with other intrathecal methotrexate treatment schedules. This confirms that the intrathecal methotrexate dose should not be based on body surface area (in fact this should not be done in patients older than 3 years). Moreover, careful monitoring of methotrexate CSF concentrations is vital for the increasing number of elderly people with meningeal carcinomatosis. These patients should have a test dose of 1 or 2 mg methotrexate in an Ommaya reservoir, with subsequent methotrexate CSF concentrations measured at 24, 48 and 72 h, and this approach may indicate the half-life of administered methotrexate.

The prolonged methotrexate half-life in our case probably caused the transient reversible neurotoxicity.

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# Interferon plus Dacarbazine in Advanced Malignant Melanoma: a Phase I–II Study

**Stein Gundersen and Asbjørn Flokkmann**

SINGLE-AGENT interferon (IFN) has limited but definite activity in metastatic malignant melanoma [1]. Whilst the synergism between IFN-α and chemotherapy is evident with several cytostatic drugs [2], dacarbazine in combination is most effective [3].

15 patients with previously non-irradiated and measurable or evaluable lesions were studied to determine the tolerability and therapeutic activity of dacarbazine and IFN-α combined in metastatic malignant melanoma. Eligibility criteria included performance status (WHO) of less than 3, life expectancy greater than or equal to 3 months and age 75 years or under.

IFN-α (Roferon-A) was administered subcutaneously daily, at an initial dose of $3 \times 10^6$ IU for the first 3 days, escalating to a maximum dose of $18 \times 10^6$ IU for the first 10 weeks, followed by $9 \times 10^6$ IU three times a week for 6 months. Dacarbazine was given intravenously once every 3 weeks, starting at 400 mg/m$^2$ with escalating doses depending on tolerance.

9 patients had lesions in lung, 6 in lung and/or skin and lymph-nodes, 1 in lung with liver metastases and 3 patients had liver metastases only. 10 patients had received chemotherapy previously. Treatment was discontinued prematurely in 2 patients due to severe influenza-like symptoms, leaving 13 evaluable patients. The criteria for response were according to WHO.

1 patient with skin metastases who had not previously responded to cisplatin, dacarbazine and vindesine had a histologically verified complete remission after 3 weeks. After 5 weeks of further treatment, the patient developed multiple skeletal metastases, still in complete remission from skin metastases. 2 patients, both previously treated by chemotherapy (5-aza-2-deoxycytidine and mitozolomide) without response, had partial remissions of lung metastases lasting for 10 and 16 weeks, respectively. 1 patient had clinical symptoms of liver failure after 3 months of treatment, and serology and computer tomography indicated that the condition was caused by IFN therapy. The patient recovered after 8 weeks without treatment.

Among 12 patients, dacarbazine (7 patients) or both dacarbazine and IFN (5 patients) were discontinued due to either leukopenia (10 patients) or severe influenza-like symptoms (2 patients). Due to leukopenia none of the patients had dose escalations of dacarbazine; therefore it is likely that the maximum tolerable dose was reached and that the intervals between courses of dacarbazine should be prolonged to 4 weeks. Considering that most patients had received chemotherapy, an

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extended phase II study in previously untreated patients is indicated.

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# Intracranial Tumours and Blood Groups

**P. Sowbhagya, V.R. Sastry Kolluri, D.K. Subba Krishna, S. Das, B.S. Das and G.N. Narayana Reddy**

THE RELATION between blood groups and diseases such as carcinoma of the stomach, peptic ulcer [1] and diabetes [2] is known. However, reports regarding blood groups and intracranial tumours [3–9] conflict. We have retrospectively studied the distribution of different blood groups in patients with intracranial tumours compared with that in the general population.

All consecutive case records of patients with histologically verified intracranial glioma, medulloblastoma, schwannoma and meningioma from 1981–1986 treated at the National Institute of Mental Health and Neurosciences, Bangalore, were reviewed and the blood groups of the patients noted. The distribution of blood groups in the general population in and around Bangalore City was obtained from the Indian Red Cross Society [10].

The total number of patients treated for intracranial tumours during the 5 years was 1287. Of these, 668 (52%) had glioma, 310 (24%) meningioma, 215 (17%) schwannoma and 94 (7%) medulloblastoma. The distribution of the four major blood groups in this population was compared with that in the general population by the $\chi^2$ test. A significantly greater proportion of patients with tumours had blood group A ($P < 0.001$), whilst more individuals in the general population had blood group O.

Of our patients with glioma, significantly more were in group A and significantly fewer in group O (both $P < 0.001$) compared with individuals in the general population. Compared with the general population, more of our patients with medulloblastoma were in groups B and AB, and the proportion was significantly higher in group B ($P < 0.001$). Contrary to this observation, Atwell [11] found no significant difference in blood group distribution in a study of children with embryonic tumours. Significantly fewer of our patients with schwannoma were in group O than the proportion in the general population, whilst most of our patients with meningioma were in blood group O or A. Yates and Pearce [9] found a higher association of meningiomas with blood group A. However, Mayer *et al.* [7] found meningiomas more frequent in group B types. Although the proportion of our group A patients with meningioma was higher than the proportion of individuals with group A in the general population, this difference was not significant.

Silverstone and Cooper [8] compared blood groups in astrocytoma patients with those in the general population. They found a significantly higher frequency of astrocytoma in group A individuals and a lesser frequency in those with group O and suggested that anti-A may provide some protection. Yates and Pearce [9] found astrocytoma less frequent in group O types and Campbell *et al.* [3] reported that glioma was more frequent in group A individuals. In contrast, Carter *et al.* [4] in a study of patients with glioblastoma and Garcia *et al.* [5] in a study of patients with astrocytoma did not find any positive correlation.

It is not known how blood group can affect the frequency of tumour in the central nervous system. Further studies of tumour immunology and blood groups are indicated.

*Table 1. Blood groups in patients with intracranial tumours and in a general population*

| | A | B | AB | O | Total |
|---|---|---|---|---|---|
| General population | 1390 (26%) | 1118 (21%) | 239 (4%) | 2682 (50%) | 5429 |
| Patients with tumours | 412 (32%) | 309 (24%) | 64 (5%) | 502 (39%) | 1287 |
| Glioma | 223 (33%) | 146 (22%) | 39 (6%) | 260 (39%) | 668 |
| Medulloblastoma | 14 (15%) | 41 (44%) | 9 (10%) | 30 (32%) | 94 |
| Schwannoma | 72 (33%) | 57 (27%) | 11 (5%) | 75 (35%) | 215 |
| Meningioma | 97 (31%) | 62 (20%) | 6 (2%) | 145 (47%) | 310 |

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