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Maturation of Neuroblastomas

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STARVATION (i.e. serum-free medium) can induce differentiation of various cell lines *in vitro* [1]. Retinoic acid and other drugs may also induce differentiation of some neuroblastoma cell lines [2, 3], and decreased N-*myc* expression precedes morphological differentiation *in vitro* [2]. Spontaneous maturation of neuroblastomas has been extraordinarily observed [4, 5]; however, it may represent the same phenomenon as spontaneous regression, i.e. undifferentiated neuroblastoma-cell kill with subsequent overgrowth of the mature ganglioneuroma tumour elements [5]. Spontaneous regression and maturation of neuroblastomas were documented in less than 2% of cases in Denmark [5].

Studies have suggested a maturational effect of specific treatment regimens of neuroblastoma [6], but the results are questionable because the possibility of cytoreduction of the most undifferentiated cells was ignored [4, 7]. A cytoreductive effect of intratumoral injection of Coley's toxin, a potent liberator of tumour necrosis factor, probably explains the case of spontaneous maturation of a neuroblastoma reported by Cushing and Wolbach [8]. Intralesional injection of interferon may induce tumour shrinkage also [9], but systemic treatment has been disappointing [9, 10].

We have studied tumour specimens in 35 of 46 consecutive neuroblastoma patients in our department from 1970 to 1980. In 7 cases, samples were retrieved from the primary tumour in the same patient both before and after adjuvant treatment. In all 4 responders, the tumour showed morphological maturation after treatment. However, in only 1 of 3 relapsing tumours was the histological picture slightly more "mature" than before treatment.

We believe that this maturational effect of treatment simply represents cytoreduction of the most undifferentiated cells in responding tumours. Therefore, studies claiming a maturational effect of specific treatments should be reviewed with caution.

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Acute Reversible Neurotoxicity after Intrathecal Low-dose Methotrexate

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CEREBROSPINAL FLUID (CSF) is a sanctuary for malignant cells during systemic chemotherapy, and may cause rapid expansion of malignancy in the central nervous system (CNS). Intrathecal administration of methotrexate results in effective drug concentrations in CSF. However, methotrexate is potentially neurotoxic, and adverse CNS effects have been described following intrathecal administration: meningoencephalitis, beginning 2–4 h after therapy and lasting 12–72 h; transient or permanent paraplegia starting 0.5–48 h (occasionally 1–2 weeks) after treatment and improving between 48 h and 2–5 months afterwards; and permanent, progressive leukoencephalopathy, occurring months to years after onset of treatment [1]. An acute transient neurological dysfunction has also been reported, occurring 1 week after the second course of high-dose intravenous methotrexate [2]. We report our case of acute transient CNS toxicity after intrathecal methotrexate administration.

A 60-year-old woman with breast carcinoma was admitted with sudden spastic ataxia of the legs. CSF analysis found meningeal carcinomatosis, and a scan of the cerebrum ruled out parenchymal metastases. An intraventricular Ommaya reservoir was applied, and methotrexate 5 mg was administered. After 1 day, neurological symptoms had disappeared and the CSF was cleared of malignant cells. After 6 days, the CSF methotrexate concentration fell below the critical level of 0.2×10^{-6} mol/l (Table 1) and a second dose of methotrexate 5 mg was given. Five days later, the patient had expressive aphasia, and neurological examination found Babinski's reflexes on both sides. CSF

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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 0.2×10^{-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 3×10^6 IU for the first 3 days, escalating to a maximum dose of 18×10^6 IU for the first 10 weeks, followed by 9×10^6 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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