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Severe Encephalopathy after High-dose Chemotherapy with Autologous Stem Cell Support for Brain Tumours

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Abstract. *Recurrent medulloblastoma carries a poor prognosis. Long-term survival has been obtained with high-dose chemotherapy with autologous stem cell transplantation and secondary irradiation. A 21-year-old woman with recurrent medulloblastoma after previous chemotherapy and radiotherapy is presented. The patient was treated with high-dose chemotherapy and autologous stem cell transplantation. She developed a severe treatment-related encephalopathy which affected her quality of life and neurocognitive functioning for the rest of her life. Possible causative factors are discussed and central nervous system toxicity by high-dose chemotherapy in brain tumour patients is reviewed. Case reports on severe central nervous system toxicity have been reported, but data from prospective studies on neurocognitive functioning are not available. These data strongly support a systematic long-term follow-up of brain tumour patients treated with high-dose chemotherapy with emphasis on neurocognitive function tests.*

Recurrent medulloblastoma carries a poor prognosis with median survival rates as low as 5 months with conventional chemotherapy (1). Despite the fact that these tumours are chemo-sensitive, long-term survival is usually not achieved with normal dosed chemotherapy. Recently, promising results have been obtained with high-dose chemotherapy followed by autologous stem cell transplantation (SCT) (2-10) (Table I). Previously described severe toxicity consisted of mucositis, myelosuppression and veno-occlusive disease (VOD) (11).

A 21 year-old female patient who experienced severe, partially irreversible treatment-related encephalopathy following high-dose chemotherapy with autologous stem cell transplantation for recurrent medulloblastoma is presented. To our knowledge, this toxicity has not been reported before in recurrent medulloblastoma.

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Key Words: Medulloblastoma, high-dose chemotherapy, autologous stem cell transplantation, encephalopathy, brain tumour, neurocognitive functioning, thiotepa, drug toxicity.

Case history

A 21 year-old young woman with recurrent medulloblastoma was admitted to the department of Medical Oncology at the University Medical Center in Nijmegen, The Netherlands, for high-dose chemotherapy and autologous stem cell transplantation after surgery.

At the age of 19, a medulloblastoma was diagnosed. After debulking surgery (tumour rest <1.5 cm^2), the patient was treated with adjuvant chemotherapy which was adjusted from the SIOP PNET III protocol (12) and consisted of vincristine 1.5 mg/m^2 weekly for 10 weeks, 4 three-weekly cycles of etoposide 100 mg/m^2 daily for 3 days, 2 three-weekly cycles of carboplatin 400 mg/m^2 on the first day of cycle (dosing schedule is in contrast with the original protocol which advised 500 mg/m^2 daily for 2 days) and 2 three-weekly cycles of cyclophosphamide 1.5 g/m^2 followed by external beam radiation therapy (35.2 Gy in fractions of 1.6 Gy at the craniospinal area and a boost on the posterior fossa of 19.8 Gy in fractions of 1.8 Gy). The patient recovered and fully resumed her daily activities. One year after treatment she developed a bilateral femoral hip necrosis for which she was treated surgically.

At the age of 21, recurrent asymptomatic local tumour activity was found on a routine MRI. Radical surgery was attempted. Additional examinations (liquor examination and MRI) revealed no craniospinal metastases or metastases outside the central nervous system (crista biopsy). Cyclophosphamide 2 g/m^2 daily for 2 days with

Table I. *Efficacy of high-dose chemotherapy with SCT for recurrent medulloblastoma in adults.*

Reference	Regimen	Patients (n)	Outcome
Dupuis-Girod *et al.* (2)	Busulfan-Thiotepa	20	50% EFS at 31 months
Mahoney *et al.* (3)	Cyclophosphamide-Melphalan	8	3 patients surviving ≥24 months
Finlay *et al.* (4)	Thiotepa-Etoposide	9	1 patient surviving 26 months
Fagioli *et al.* (5)	Thiotepa-Etoposide	8	2 patients surviving ≥55 months
Papadakis *et al.* (6)	BCNU-Thiotepa-Etoposide	2	Survival < 24 months
Abrey *et al.* (7)	Variable: Carmustine-Etoposide-Thiotepa-Carboplatin	11	2 yr EFS: 54.5%
Zia *et al.* (8)	Carboplatin-Etoposide-Cyclophosphamide	6	2 patients with longer EFS (19-24)
Graham *et al.* (9)	Cyclophosphamide-Melphalan	19	4 patients with longer EFS (27-47 months)
Dunkel *et al.* (10)	Carboplatin-Thiotepa-Etoposide	23	34% EFS at 36 months

EFS: event-free survival.

mesna followed by granulocyte colony stimulating factor (G-CSF) was administered and stem cells were harvested successfully by leukapheresis. This initial treatment phase was complicated by a pneumothorax after insertion of a central venous catheter and neutropenic fever treated with antibiotics. Bacterial cultures were negative.

The myelo-ablative chemotherapy, based on the schedule used by Dunkel *et al.* (10) consisted of carboplatin 500 mg/m^2 or AUC 7 daily for 3 days, thiotepa 300 mg/m^2 daily for 3 days and etoposide 100 mg/m^2 daily for 3 days. The carboplatin dose was calculated with the Calvert formula in which the measured creatinine clearance was used. The measured creatinine clearance was considerably lower than the Cockroft calculated creatinine clearance with values of 80 and 100 ml/min, respectively; the latter is generally used in the Calvert formula. On the 9th day after the start of chemotherapy, autologous stem cells were infused. At that time the patient suffered from severe mucositis, skin toxicity, diarrhoea and fever. She was treated with total parental nutrition, antibiotics, anti-viral and anti-fungal agents. Extensive cultures were negative. Ten days after stem cell re-infusion her granulocyte count recovered, and antibiotics were discontinued. Two days later the patient developed a high fever, hypotension and a pleural and pericardial effusion. Sepsis was suspected and antibiotics were started. Blood cultures became positive for a corynebacterium species. Additional blood examination showed an increased alkaline phosphatase (111 U/L), γ-glutamyl-transpherase (252 U/l) and hyperbilirubinemia (119 umol/l). Additional investigations which included an echocardiography, cerebral, abdominal and thoracic computer tomography and MRI of the brain were negative for the presence of abcesses, cardiomyopathy, progressive medulloblastoma and of veno-occlusive disease. Although her temperature returned to normal in the next 2 weeks, 23 days after autologous stem cell re-infusion she became bradyphrenic, hypertonic, anxious and was not able to swallow. An EEG showed changes compatible with an encephalopathy. MRI showed cortical atrophy without tumour relapse. There were no new grey or white matter alterations. Bacterial, virological and aseptic meningitis/encephalitis, tumour relapse and metabolic disturbances were excluded by MRI, blood en liquor examinations, including serological virological tests, viral cultures and liquor PCR's (polymerase chain reaction). She remained in a vegative state for almost 2 months during which period her condition showed no significant improvement. She was transferred to a revalidation clinic where she recovered only partially in the following months. Although cognitive problems remained present, she regained the ability to talk, eat, sit, walk and communicate. Fourteen months after peripheral stem cell re-infusion, she complained about headaches, nausea and vomiting. MRI showed a hydrocephalus due to a tumour relapse in the posterior fossa. She died one month later.

Discussion

We present a patient with recurrent medulloblastoma who suffered from severe and only partially reversible encephalopathy after treatment with high-dose chemotherapy and autologous SCT.

In studies which evaluated the efficacy and safety of high-dose chemotherapy with SCT in children and adults with high-risk brain tumours, multi-organ system failure (MOF), infections, veno-occlusive disease (VOD) and haemorrhage have been reported as the most frequent causes of death (Table II). Treatment-related mortality varied between 0 and 21% and was higher in adult patients (11). Encephalopathy was reported in 3 (4, 6, 16) out of 10 studies in which children as well as adults were included (Table II). The ages at which patients developed encephalopathy in these studies were not recorded. Central nervous system toxicity was usually reversible and not considered to be a major problem. In none of the studies was functional ability status assessed after high-dose chemotherapy. Fagioli *et al.* (5) reported that 8 out of

Table II. *Toxic deaths and central nervous system toxicity in studies with high-dose chemotherapy with autologous SCT in children and adults with central nervous system tumours.*

Study	Patients (n), median age (range)	TD (%)	Cause of toxic death (n)	Central nervous system toxicity (n)
			Studies in children and adults	
Pérez-Martínez *et al.* (13)	N=7, 2 (1-4) years	0	–	–
Broniscer *et al.* (14)	N=17, 2 (1-31) years	12	Sepsis (1), meningitis (1)	Seizures (2)
Finlay *et al.* (4)	N=45, 8 (0-36) years	16	Intatum. haemorrhage (1), sepsis (2), endotoxic shock (1), VOD (2), MOF with encephalopathy (1)	Encephalopathy (1), transient somnolence with disorientation and short-term memory loss
Graham *et al.* (9)	N=49, 9 (0-27) years	2	Aspergillus (1)	Seizure (1)
Mahoney *et al.* (3)	N=19, 10 (2-16) years	21	Pulm. haemorrhage (1), sepsis (2), meningitis (1)	None
Bouffet *et al.* (15)	N=22, 10 (4-20) years	9	pneumonitis (1)	Headache (7), drowsiness (5), hallucinations (3), seizures (1)
Fagioli *et al.* (5)	N=27, 11 (3-19) years	4	Candida pneumonia	None
Dunkel *et al.* (10)	N=23, 12 (1-35) years	13	MOF (2), Aspergillus infection/VOD (1)	Grade III :confusion, hallucinations (4) Grade IV: coma, seizures, psychosis (1)
Papadakis *et al.* (6)	N=42, 12 (0-46) years	21	Resp. failure (3), pulm. haemorrhage (1), renal failure (1), infection (2), brainstem necrosis (1)	22 episodes (seizures, haemorrhage, paresis, headache, encephalopathy, hallucinations) in 15 patients: 17 reversible; remainder commonly an early indication of progression
Papadopoulos et al. (16)	N=31, 27 (2-57) years	3	Sepsis (1)	Mental status changes (7), seizures (5), reversible encephalopathy (2)
			Studies in adults only	
Zia et al. (8)	N=6, 29 (21-35) years	–	–	Drowsiness (1), non-communicativeness without focal neurological signs (1), MRI enhancing lesions surrounded by edema (1)
Abrey *et al.* (7)	N=45, 30 (18-47) years	18	MOF (5), VOD (3)	–
Cairncross *et al.* (17)	N=20, 46 (28-57) years	20	Encephalopathy (3), intratum. haemorrhage (1)	Encephalopathy (5)

TD: Toxic death; VOD: veno-occlusive disease; MOF: multiple organ system failure.

11 children after high-dose chemotherapy for recurrent medulloblastoma attended school, suggesting an acceptable quality of life. However, no details on type of school or intellectual functioning were provided. Central nervous system toxicity was observed in 2 (8, 17) out of 3 (7, 8, 17) studies conducted in adult patients only (Table II). The more frequent report of encephalopathy in 'adult' studies suggests increased neurotoxicity with age. In the first study by Cairncross *et al.* (17), who studied high-dose thiotepa and autologous stem cell rescue in adult patients suffering from recurrent oligodendrogliomas, encephalopathy was observed in 25% of patients. In this study, 3 patients died from encephalopathy, which in 2 cases was accompanied by a wasting syndrome. The thiotepa was considered to be responsible for this severe encephalopathy. Thiotepa-induced encephalopathy was also reported in breast cancer patients treated with high-dose chemotherapy (18, 19). Thiotepa is lipid-soluble, alkylating agent which has the ability to penetrate the brain. The pathophysiological mechanisms involved in thiotepa-induced encephalopathy are unknown. Thiotepa-related encephalopathy is characterized by inappropriate behavior, loss of memory, confusion, and somnolence (20). The lowest dose at which encephalopathy occurred is 900 mg/m^2, with an incidence of 5%. At a dose of 1,125 mg/m^2 the incidence of encephalopathy may increase to approximately 15% (20, 21).

The second study, published by Zia *et al.* (8), included 1 out of 6 patients with recurrent medulloblastoma who

experienced an inflammatory syndrome which included an encephalopathy. The inflammatory syndrome in this patient was thought to be caused by the administration of a high dose of carboplatin (dose based on Calvert formula with measured creatinine clearance of 230 ml/min and area under curve (AUC) of 21). Dunkel and Finlay (11) reported that a substantial proportion of the observed toxic death rate with high dose chemotherapy and autologous stem cell transplantation in brain tumours is due to a capillary leak syndrome (symptoms may include encephalopathy), which occurs more frequently when carboplatin is dosed on a body surface area basis rather than using the Calvert formula. The decreased creatinine clearance measured in our patient might have contributed to the observed neurotoxicity due to impaired clearance of carboplatin and thiotepa.

The patient presented in our report was 21 years of age when she was treated with high-dose thiotepa, carboplatin and etoposide for recurrent medulloblastoma. Bacterial and viral agents have to be considered when neurological symptoms develop after stem cell transplantation. Bacterial cultures, viral cultures and viral PCR's of liquor and serum including herpes simplex, varicella zoster and human herpes virus 6, were not supportive of the presence of a bacterial or viral infection.

Limbic encephalitis is a well-known paraneoplastic syndrome and may present with similar symptoms as those seen in our patient (22). In the majority of patients suffering from a limbic encephalitis, characteristic MRI findings are present (22). These include unilateral or bilateral mesial temporal lobe abnormalities that show enhanced signal on T2 weighted images (22). Furthermore, inflammatory changes in the liquor as well as the presence of auto-antibodies support this diagnosis. Although no antibodies were measured in the liquor or serum of our patient, the absence of characteristic MRI findings in addition to the absence of inflammatory findings in the liquor make the diagnosis limbic encephalitis in our patient less likely. In light of these findings, in addition to the absence of metabolic derangements and concomitant drug toxicity which are other common causes of encephalopathy after stem cell transplantation, we considered the encephalopathy related to the high-dose chemotherapy and to thiotepa, in particular. Factors which may have contributed were her previous extensive treatments with chemotherapy and radiotherapy, adult age, and lower creatinine clearance as expected for a young woman which might have impaired clearance of carboplatin and thiotepa.

After conventional first-line treatment which includes surgery and radiotherapy, impaired intelligence has been found in nearly 90% of treated medulloblastoma patients (23). Young age at the time of treatment as well as a higher radiotherapy dose seem to be risk factors for a lowered intelligence quotient (24). Maddrey *et al.* (25) assessed cognitive performance and psychosocial functioning in 16 medulloblastoma survivors (mean age at diagnosis: 7.2 years) in the second decade after diagnosis and found significant impairments in all neuropsychological and psychosocial domains in more than 50% of survivors.

Although the life expectancy of recurrent medulloblastoma patients may be increased with high-dose chemotherapy with autologous SCT, none of the studies reported to date have systematically included short-term and long-term follow-up of quality of life and functional (neuro-cognitive and psychosocial) performance.

Disabling cognitive dysfunction has been described after treatment with high-dose methotrexate-based chemotherapy and whole brain radiotherapy for central nervous system lymphoma (26). Furthermore, (sub)acute encephalopathy (27) as well as late cognitive dysfunction (28) have been observed as complications of high-dose chemotherapy in breast cancer patients. Hensel *et al.* (29) evaluated the quality of life, with special emphasis on rehabilitation in social and professional life, in 304 long-term survivors after high-dose chemotherapy and SCT and found that this treatment had an unfavourable impact on the quality of life, including re-integration into social and professional life during 3-6 years after which most symptoms and scores returned to normal.

We strongly recommend standard long-term follow-up of patients treated with high-dose chemotherapy and SCT for brain tumours with special emphasis on neurocognitive function. These data should be available and should be taken into account in the final decision whether and how to treat recurrent medulloblastoma.

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