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Case Report

Fatal Radiation Myelopathy After High-dose Busulfan and Melphalan Chemotherapy and Radiotherapy for Ewing's Sarcoma: A Review of the Literature and Implications for Practice

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ABSTRACT:
Radiation myelopathy is a rare, devastating, late effect of radiotherapy to the spinal cord. Spinal cord tolerance is currently accepted as about 50 Gy in 1.8–2 Gy fractions. However, the effect of chemotherapy on cord tolerance is unclear. This issue is important, given the increasing use of chemotherapy in combination with radiotherapy. We describe the case of a 17-year-old boy with a right apical paraspinal Ewing's tumour in the neck treated with induction chemotherapy, high-dose chemotherapy (busulfan and melphalan) with peripheral stem-cell rescue and, 4 months later, radiotherapy to the primary tumour site (cervical cord received 50 Gy in 30 fractions). After a latent period of 4 months, he developed a progressive, severe and ultimately fatal radiation myelopathy, which we suggest was due to a synergistic interaction between the high-dose chemotherapy and the radiotherapy. The use of such chemotherapy regimens in Ewing's tumours should be carefully considered, particularly when radiotherapy encompassing the spinal cord is an essential component of management. Seddon, B. M. *et al*. (2005). *Clinical Oncology* **17,** 385–390

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Introduction

Radiation myelopathy is a late effect of therapeutic irradiation that has been recognised for over 50 years [1–3]. Effects are seen in the irradiated segment of the spinal cord, and may occur in acute transient or delayed permanent forms. In the acute syndrome, electric shock-like sensations radiating to the extremities are experienced on neck flexion (Lhermitte's sign). These typically occur 2–4 months after radiotherapy, and resolve completely with no specific treatment [4–6]. Lhermitte's sign has been reported after radiotherapy doses from 30 Gy, although the incidence increases with doses above 50 Gy [4,5]. In contrast, delayed radiation myelopathy manifests as a progressive irreversible decline in motor and sensory function of the limbs associated with bladder and bowel dysfunction, which usually occurs at least 6 months after radiotherapy [7,8]. Because the clinical findings are indistinguishable from other causes of myelopathy, certain criteria must be fulfilled to make a diagnosis of radiation myelopathy: other causes must be excluded, the clinical presentation must be consistent with radiation myelopathy, and the dose and timing of radiation must be consistent with a spinal cord radiation injury [1].

Literature reviews have indicated that the risk of myelitis associated with doses of 55–61 Gy and 69–73 Gy is 5% and 50% at 5 years, respectively [1,9]. It has been suggested that 50 Gy is an acceptable upper limit when attempting tumour cure, and that doses of 60 Gy may be considered in

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extreme cases, such as when the cord is threatened by tumour growth [1].

These dose limits apply to the use of radiotherapy alone. However, increasingly, radiotherapy is being used in combination (either before, after or concurrently) with chemotherapy. Furthermore, the use of high-dose chemotherapy with blood stem-cell support in treatment regimens is becoming more frequent. The effect of chemotherapy, at conventional and especially at high doses, on the tolerance of the spinal cord to radiation is not well understood. We describe a case of a patient with Ewing's sarcoma who was treated with radiotherapy after high-dose chemotherapy and who developed radiation myelopathy despite a radiation dose that lay within conventionally accepted tolerance limits.

Case History

A 17-year-old boy presented with a 4-month history of paraesthesiae in the right hand. Clinical examination revealed pyramidal weakness, reduced sensation, reduced tone, depressed reflexes in the right arm and a right-sided Horner's Syndrome. A chest X-ray showed a mass in the right lung apex, and computed tomography (CT) confirmed a right apical mass infiltrating the right brachial plexus (Fig. 1a). Magnetic resonance imaging (MRI) revealed a $14 \times 7 \times 8$ cm mass in the right paravertebral gutter extending from the C5 to T3 vertebrae, invading the right-sided paraspinal muscles, displacing the trachea and abutting the aortic arch inferiorly. There was extensive intraspinal extension with a large extradural mass effacing the thecal sac. Biopsy showed a malignant round cell tumour of Ewing's/primitive neuroectodermal type. Staging investigations carried out to exclude metastatic disease (bone scan, bone marrow aspirate and trephine, and CT thorax) were normal.

The boy was registered on the EuroEwing99 study and, according to protocol, was treated with six cycles of VIDE chemotherapy given three times a week: vincristine 1.5 mg/m^2 by bolus injection on day 1, ifosfamide 3 g/m^2 by continuous iv infusion over 1 h for 3 consecutive days (total dose 9 g/m^2), doxorubicin 20 mg/m^2 by continuous iv infusion over 4 h for 3 consecutive days (total dose 60 mg/m^2) and etoposide 150 mg/m^2 by continuous iv infusion over 4 h for 3 consecutive days (total dose 450 mg/m^2). Magnetic resonance imaging after the first two cycles confirmed considerable reduction in tumour size, although an $8 \times 5 \times 4$ cm residual mass remained. However, imaging after four and six cycles showed no further interval change in tumour size. On completion of six cycles, the boy experienced some improvement in neurological function of his right arm, but there was still significant impairment. He received a single cycle of VAI chemotherapy: vincristine 1.5 mg/m^2 by bolus injection on day 1, actinomycin 0.75 mg/m^2 by bolus iv injection for 2 consecutive days (total dose 1.5 mg/m^2), ifosfamide 3 g/m^2 by continuous iv infusion over 1 h for 2 consecutive days (total dose 6 g/m^2). He was then randomised to receive

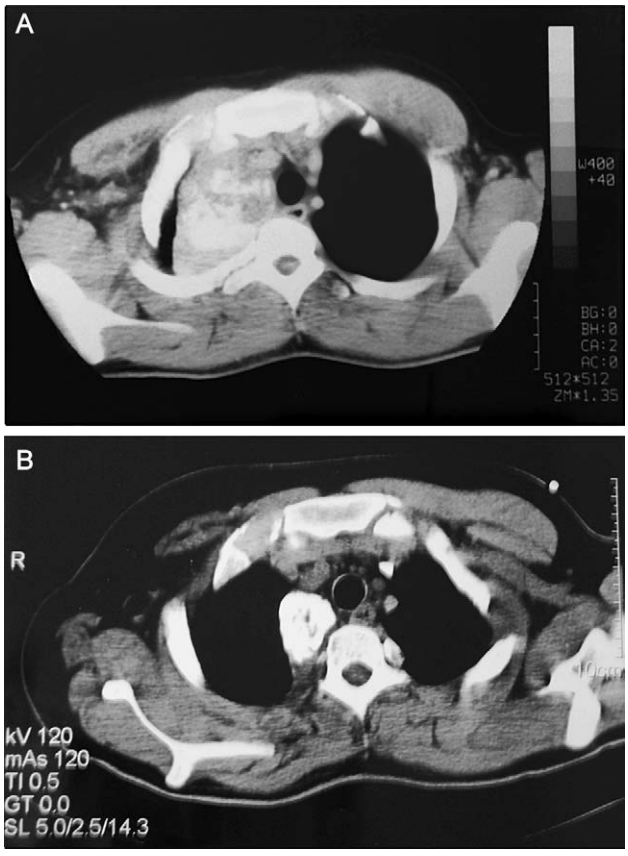

Fig. 1 – (a) Computed tomography of the thorax showing a tumour mass located at the right lung apex; (b) computed tomography of the thorax carried out 2 months after induction chemotherapy and high-dose chemotherapy, showing a calcified residual tumour mass located at the right lung apex.

high-dose chemotherapy with autologous stem-cell rescue. This consisted of busulfan 600 mg/m^2 (given orally in four divided doses on day −6 to day −3), melphalan 140 mg/m^2 (given by continuous iv infusion over 30 min on day −2), and stem cell infusion on day 0. The post-transplant period was unremarkable. A CT scan carried out 2 months later showed only a 3.5 cm calcified residual mass in the right paravertebral gutter (Fig. 1b), which showed no uptake on FDG-PET scanning. Surgical removal of this mass was not possible without significant damage to the adjacent brachial plexus. He therefore received radiotherapy as local tumour treatment, starting 4 months after high-dose chemotherapy.

The boy underwent CT planning positioned supine with the neck extended, immobilised in a rigid plastic cast. He was planned and treated in two phases. In phase I, the planning target volume (PTV) was defined as the pre-chemotherapy gross tumour volume (GTV), with a radial margin of at least 1.5 cm. Treatment of the PTV was achieved using anterior and posterior opposed portals (22.8 cm in length), including the spinal cord between C1 and T6 vertebrae (Fig. 2a,b). In phase one, PTV was treated to 50.1 Gy in 30 fractions of 1.67 Gy over 49 days. In phase two, the PTV was defined as the post-chemotherapy GTV