ELSEVIER

European Journal of Cancer 41 (2005) 1588–1596

European Journal of Cancer

www.ejconline.com

Late magnetic resonance imaging features of leukoencephalopathy in children with central nervous system tumours following high-dose methotrexate and neuraxis radiation therapy

Stewart J. Kellie [a,b,*], Jyoti Chaku [a,b], Liane R. Lockwood [c], Peter O'Regan [c], Keith D. Waters [d], Christopher K.F. Wong [e], on behalf of the Australian and New Zealand Children's Haematology Oncology Group

[a] *Discipline of Paediatrics, University of Sydney, Sydney, NSW, Australia*
[b] *Department of Oncology, Children's Hospital at Westmead, Sydney, NSW, Australia*
[c] *Department of Haematology and Oncology, Royal Children's Hospital, Brisbane, QLD, Australia*
[d] *Department of Haematology and Oncology, Royal Children's Hospital, Melbourne, VIC, Australia*
[e] *Department of Radiology, Children's Hospital at Westmead, Sydney, NSW, Australia*

Received 29 September 2004; received in revised form 6 January 2005; accepted 25 February 2005
Available online 27 April 2005

Abstract

High-dose methotrexate (HDMTX) is used increasingly to treat children with central nervous system (CNS) tumours. Although the neuro-imaging features of leukoencephalopathy associated with systemic or intrathecal methotrexate administered after cranial radiation have been well described, the extent to which the sequencing of HDMTX prior to cranial radiation in infants and children predisposes to late neuroradiological features of leukoencephalopathy is unknown. This report describes the National Cancer Institute (NCI) toxicity grade of leukoencephalopathy based on magnetic resonance imaging (MRI) findings in all patients who survived 4 or more years after treatment on an earlier phase II study. These patients, with newly diagnosed CNS embryonal tumours, were in the age range 3.5–14.2 years (median 6.9 years) at diagnosis, and received four courses of pre-irradiation combination chemotherapy, including HDMTX 8 g/m^2. Following completion of the 'up-front' phase II study, all patients received conventionally fractionated whole brain doses of 36–50.4 Gy. The radiation dose and treatment volumes were determined individually according to the primary tumour location and results of extent of disease evaluations. The most recent MRI brain scans, obtained 4.0–10.5 years (median 6.5 years) after radiation therapy and comprising a minimum of T1, T1 following gadolinium and T2 sequences, were reviewed centrally to assess the neuroradiological grade of leukoencephalopathy, based on the NCI Common Terminology Criteria for Adverse Events, v3.0. Grade I changes (mild increase in subarachnoid space, and/or mild ventriculomegaly, and/or small/focal T2 hyperintensities) were evident in 8 of the 12 patients and grade II changes (moderate increase in subarachnoid space and/or moderate ventriculomegaly, and/or focal T2 hyperintensities extending to the centrum ovale) were found in the remaining 4. In conclusion, treatment with multiple courses of HDMTX prior to 36–50.4 Gy cranial radiation did not result in moderate to severe MRI features of leukoencephalopathy. Future studies in paediatric neuro-oncology patients, involving HDMTX combined with prospective neuropsychological evaluations appear justified.

Keywords: Medulloblastoma; Methotrexate; Leukoencephalopathy; Radiation therapy

* Corresponding author. Tel.: +61 2 9845 2141; fax: +61 2 9845 2171.
E-mail address: stewartk@chw.edu.au (S.J. Kellie).

0959-8049/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2005.02.024

1. Introduction

Methotrexate [1–5] and cranial radiation [6–12], either separately or together [5,13–22], have been associated with clinical or neuroradiological evidence of leukoencephalopathy in survivors of childhood leukaemia and central nervous system (CNS) or head/neck tumours. The incidence and severity of magnetic resonance imaging (MRI) appearances of leukoencephalopathy seems to increase with radiation dose and younger age [8,12,23]. Reduced normal-appearing white matter volumes (NAWM) among children surviving treatment for brain tumours have been associated with decreased attentional abilities, leading to declining intelligence quotient (IQ) and academic achievement [23].

Evidence of leukoencephalopathy has also been documented in patients receiving chemotherapy without cranial radiation [3,14,18,24]. Allen observed in a case report that high-dose methotrexate (HDMTX) with citrovorum factor rescue in the absence of cranial radiation could lead to clinical and computed tomography (CT) evidence of leukoencephalopathy. A decade later, Allen and colleagues reported two instances of leukoencephalopathy (transient in one) among 10 patients with CNS tumours receiving four courses of HDMTX 8 g/m^2 prior to cranial radiation therapy [14].

The relationship between CT or MRI features of leukoencephalopathy and significant neurological or neuropsychological decline have been inconsistent [26] or negative [21,25,27,28]. Other studies of white matter loss and neurocognitive deficits in children with medulloblastoma [12,13,23,25] and the relationship between neuroradiological findings and neuropsychological outcomes in children with leukaemia [20] have demonstrated at least a partial correlation between some aspects of neuropsychological function and neuroimaging findings, especially abnormalities demonstrated on MRI scanning.

The current study extends the phase II observations of our earlier study [29] and explores the incidence and severity of late neuroradiological features of leukoencephalopathy in children with high-risk CNS embryonal tumours receiving HDMTX immediately prior to craniospinal radiation therapy [29]. Our study failed to demonstrate more serious evidence of leukoencephalopathy than has been commonly associated with cranial radiation alone. Because of the original design of our upfront phase II study, which comprised mostly 'high-risk' patients with CNS embryonal tumours, a control population comprising children treated with radiation alone was not feasible.

2. Patients and methods

Patients with previously untreated newly diagnosed CNS embryonal tumours were originally enrolled on a neoadjuvant phase II study comprising four courses of carboplatin, etoposide and HDMTX conducted by the Australian and New Zealand Children's Haematology Oncology Group during the 1990s. The results of this study have been published [29]. Updated outcome data are provided for general interest only as the details of radiation treatment and the selection of post-radiation chemotherapy was at the discretion of the treating physician. Of the patients who received craniospinal radiation therapy and after a median follow-up of 8.1 years, the 5-year progression free (PFS) and overall survival (OS) for patients with medulloblastoma was 0.67 (SEM 0.14) and 0.83 (SEM 0.11), respectively, and for primitive neuroectodermal tumour (PNET)/pineoblastoma; 0.29 (SEM 0.17) and 0.43 (SEM 0.19), respectively.

The MRI-leukoencephalopathy status of all patients who received craniospinal radiation and survived 4 years or more are included in this report. Patients were monitored by periodic MRI scanning, comprising a minimum of T1, T2 and T1 with gadolinium sequences and the most recent MRI brain study from each patient was centrally reviewed by three of us (CKFW, SJK, JC) and graded according to the neuroimaging leukoencephalopathy toxicity grading criteria defined by the National Cancer Institute Common Terminology Criteria for Adverse Events, (NCI CTCAE), Version 3.0 (Table 1). All participants or their guardians provided signed informed consent at the time of diagnosis after reviewing written information about the study, including details of follow-up investigations, in accordance with Institutional Ethics Committee requirements at each participating centre.

The treatment outline of the neoadjuvant phase II component of the original study is outlined in Table 2. The HDMTX infusion was administered over 4 h in 350 ml/m^2 of 5% dextrose with 1 mmol/kg $NaHCO_3$. At the completion of the HDMTX infusion, intravenous (i.v.) fluids at a rate of 2000 ml/m^2 were continued for at least 20 h and up to 48 h to maintain urine output. Leucovorin rescue (folinic acid) 10 mg orally every 6 h for 16 doses was commenced 24 h from the start of the HDMTX infusion. Additional leucovorin was used if the systemic MTX concentration exceeded 1×10^{-5} M at 24 h or $>3 \times 10^{-6}$ M at 48 h or until MTX concentrations fell below 5×10^{-7} M.

The characteristics of the patients are listed in Table 3. Scans from all 12 long-term survivors, aged 3.2–14.2 years at diagnosis, (median 6.6 years), who received craniospinal radiation therapy after completing the neoadjuvant phase II study were available for retrospective review. The follow-up interval from the time of radiation treatment to the most recent brain MRI study ranged from 4.0 to 10.5 years, (median 6.9 years). One patient (number 11) received additional frontal radiation therapy for a subfrontal recurrence of medulloblastoma 7.5 years prior to his most recent MRI brain scan.