European Journal of Cancer (2015) **51**, 2634–2642

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journal homepage: www.ejcancer.com

Intraventricular methotrexate as part of primary therapy for children with infant and/or metastatic medulloblastoma: Feasibility, acute toxicity and evidence for efficacy

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Received 4 December 2014; received in revised form 27 July 2015; accepted 12 August 2015
Available online 4 September 2015

KEYWORDS
Methotrexate
Intraventricular
Medulloblastoma
Brain tumours
Chemotherapy
Treatment

Abstract ***Background:*** To assess feasibility, acute toxicity, and efficacy of intraventricular methotrexate administered as part of the primary therapy in medulloblastoma.
Methods: From 2001 to 2007, 240 patients <22 years from 61 treatment centres were registered. Patients received 2–3 cycles of intraventricular methotrexate with systemic chemotherapy in three different treatment arms of the prospective multicentre trial HIT2000 (150 children >4 years with metastatic, 59 <4 years with non-metastatic, 31 <4 years with metastatic medulloblastoma).
Results: 211 patients received an intraventricular access device with a subcutaneous reservoir for the application of chemotherapy. Reservoir-associated complications were documented in

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http://dx.doi.org/10.1016/j.ejca.2015.08.009

57 (27%) patients, mostly due to infection ($n = 32$) and reservoir malfunction ($n = 19$), requiring removal in 39 (18%) patients. Acute neurotoxicity likely associated with intraventricular MTX was observed in 9/202 documented patients. Toxicity was usually mild, apart from one therapy-associated death due to toxic oedema followed by seizures. Of 519 treatment cycles including intraventricular methotrexate, 226 (43%) were reduced or omitted, most frequently due to the absence of an intraventricular device. Survival rates were higher in patients receiving $\geqslant 75\%$ of the scheduled intraventricular methotrexate dose compared to those receiving $<75\%$ in both univariate and multivariate models (event-free survival (EFS), 61.5 versus 46.2%, $p = 0.004$; OS, 75.5% versus 60.4%, $p = 0.015$; hazard ratio: EFS 1.723, $p = 0.016$; OS 1.648, $p = 0.051$).

Conclusion: Intraventricular methotrexate therapy was feasible and mostly well tolerated. Infections were the most frequent complication. A higher cumulative dose of intraventricular methotrexate was associated with better survival. Further evaluation of efficacy and late effects is warranted.

1. Introduction

Medulloblastoma (MB) is the most common malignant brain tumour in childhood [1]. Young age, disseminated disease, residual tumour in patients without dissemination, and biological parameters are major prognostic factors [2–7]. Survival rates have raised continuously over the last decades [8–11]. Because of frequent dissemination via the cerebrospinal fluid (CSF), craniospinal radiotherapy (CSI) is important backbone of multimodal treatment. Due to the high vulnerability to radiotherapy-induced cognitive deficits, MB treatment in children younger than 3–5 years is particularly difficult [8,12,13]. To reduce these deficits, recent regimens tried to avoid or delay radiotherapy in young children by intensified postoperative chemotherapy [6,14–17], and/or addition of intraventricular chemotherapy to intravenous chemotherapy. In the HIT-SKK1992 trial of the Society of Pediatric Oncology and Hematology in Germany, Austria and Switzerland (GPOH) intraventricular methotrexate (i.vc. MTX) was introduced to substitute radiotherapy in children younger than 3 years with MB [6]. Neurocognitive outcome was better compared to the previous, CSI including trial HIT-SKK1987, and survival rates improved, particularly for desmoplastic MB [18]. These results were confirmed for non-disseminated MB under the age of 4 in the subsequent study HIT‘2000 [15].

When administered directly into the CSF via intraventricular access device (IVAD), sustained cytotoxic MTX CSF-levels can be achieved [19]. Compared to repeated lumbar punctures (LP), intraventricular therapy is convenient, painless, and relatively safe [20]. However, several complications have been reported, including infection, haemorrhage, oedema or technical problems (e.g. misplacement or malfunction) [20–22]. Infections may be associated with both implantation and treatment application and are usually caused by *Staphylococcus epidermidis* [20,23]. Serious complications which require removal and reimplantation of the reservoir appear to be infrequent in previous studies analysing older patients [20,23], but information on complications in younger children is rare [8,15].

MTX can cause neurotoxic effects by direct toxicity to the central nervous system (CNS) and the influence on diverse biochemical pathways [24]. MTX-induced neurotoxicity is classified into acute (during or within hours), subacute (after days to weeks) and chronic (after months to years) forms. Acute neurotoxicity (seizures, confusion, somnolence and chemical arachnoiditis) is supposed to be related to peak MTX-CSF-levels and the total MTX dosage [24,25]. Bleyer et al. [25] reported reduced acute neurotoxicity rates when MTX was given in a “concentration × time” regimen compared to higher, single injections of MTX. In addition, the “concentration × time” schedule achieved a longer therapeutically effective concentration of MTX in the CSF. Subacute neurotoxicity usually manifests as encephalopathy and myelopathy. Learning disabilities, a decrease in intelligence, and leukoencephalopathy are considered symptoms of chronic MTX-associated neurotoxicity [24].

Here, we evaluate the feasibility and acute toxicity of intraventricular MTX treatment in children and young adults with metastatic and non-metastatic MB treated within the prospective multicentre trial HIT‘2000. Explorative efficacy analyses assessing the effect of intraventricular MTX treatment on survival are reported.

2. Patients and methods

2.1. Eligibility

The HIT2000 trial (NCT00303810) was approved by the ethics committee of the University of Wuerzburg. All patients or legal representatives gave their written informed consent before participation. Patients were included in this study if they had histologically confirmed