European Journal of Cancer 76 (2017) 188–196

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Feasibility, toxicity and response of upfront metaiodobenzylguanidine therapy therapy followed by German Pediatric Oncology Group Neuroblastoma 2004 protocol in newly diagnosed stage 4 neuroblastoma patients

K.C.J.M. Kraal [a,f,*,1], G.M. Bleeker [b,1], B.L.F. van Eck-Smit [c], N.K.A. van Eijkelenburg [f], F. Berthold [d], M.M. van Noesel [e,f], H.N. Caron [a], G.A.M. Tytgat [a,f]

[a] *Department of Pediatric Oncology, Emma Children's Hospital, Amsterdam, The Netherlands*
[b] *Department of Radiology/Nuclear Medicine, NWZ Alkmaar, Alkmaar, The Netherlands*
[c] *Department of Nuclear Medicine, Academic Medical Centre (AMC), Amsterdam, The Netherlands*
[d] *Department of Pediatric Oncology and Hematology, University Children's Hospital, Center for Molecular Medicine Cologne (CMMC), Cologne, Germany*
[e] *Department of Pediatric Oncology/Hematology, Erasmus MC (EMC)-Sophia Children's Hospital, Rotterdam, The Netherlands*
[f] *Princess Máxima Centre for Pediatric Oncology, Utrecht, The Netherlands*

Received 3 March 2016; received in revised form 27 September 2016; accepted 6 December 2016

KEYWORDS
^{131}I-MIBG (meta-iodobenzylguanidine); NBL (neuroblastoma)

Abstract ***Aim of the study:*** Radiolabelled meta-iodobenzylguanidine (MIBG) is an effective option in treatment of neuroblastoma (NBL) tumours. We studied feasibility, toxicity and efficacy of upfront ^{131}I-MIBG and induction treatment in stage 4 NBL patients.
Patients and methods: Retrospective, multi-centre (AMC and EMC) pilot regimen (1/1/2005–2011). Newly diagnosed stage 4 NBL patients, were treated with 2 courses of ^{131}I-MIBG, GPOH 2004 NBL protocol, myeloablative therapy (MAT) and autologous stem cell rescue (ASCT). ^{131}I-MIBG was administered in a fixed dose. Response rate (RR) was defined as complete remission, very good partial response and partial response.
Results: Thirty-two patients, (median age [range] 2.9 [0–11.4] years), 21 received ^{131}I-MIBG therapy, 11 did not because of: MIBG non-avid (N = 5) and poor clinical condition

Financial support: Stichting Kinderen Kankervrij (KIKA).
* *Corresponding author*: Pediatric Oncologist, AMC, Meibergdreef, Amsterdam, The Netherlands.
E-mail address: K.C.J.Kraal@prinsesmaximacentrum.nl (K.C.J.M. Kraal).
[1] The first two authors have contributed equally to this article (joint first authorship).

http://dx.doi.org/10.1016/j.ejca.2016.12.013

(N = 6). In 95% of eligible patients ^{131}I-MIBG treatment was feasible within 2 weeks from diagnosis. Interval between chemotherapy courses was 25 days (^{131}I-MIBG group) versus 22 days (chemotherapy group). No stem cell support was needed after ^{131}I-MIBG therapy. Stem cell harvest in both groups was feasible, neutrophil recovery was comparable, but platelet recovery post MAT, ASCT was slower for ^{131}I-MIBG-treated patients. RR post ^{131}I-MIBG was 38%, post MAT + ASCT was 71% (^{131}I-MIBG group), 36% (chemotherapy group) and overall 59%. ***Conclusions:*** Induction therapy with ^{131}I-MIBG before the HR GPOH NB 2004 protocol is feasible, tolerable and effective in newly diagnosed stage 4 NBL patients. ^{131}I-MIBG upfront therapy induces early responses.

1. Introduction

Neuroblastoma (NBL) is the most common extra cranial solid tumour in childhood, derived from the sympathetic nervous system [1]. The prognosis for patients with HR NBL, was less than 40% for a long time, but this has improved over the last decades [2,3]. A study performed by Yu *et al.* [4] showed a 20% survival (overall survival [OS] and event free survival [EFS]) benefit of addition of immunotherapy after myeloablative therapy (MAT), followed by autologous stem cell transplantation (ASCT) in HR NBL patients. The 3-year EFS of HR NBL patients, treated according to the German Pediatric Oncology Group (GPOH) NB 97 protocol with ASCT has been shown to be 47% [5].

Imaging with ^{123}I-meta-iodobenzylguanidine ^{123}I-(MIBG) is a reliable and reproducible method for staging and response evaluation in NBL [6–8]. For targeted treatment, MIBG labelled with ^{131}I has been used successfully [9]. ^{131}I-MIBG has a significant antitumour efficacy against NBL, with response rates (RRs) between 20% and 60% [10–16]. Tandem ^{131}I-MIBG therapy can be given to patients with relapsed/refractory NBL with tumour response or stable disease, and available stem cells. Early second ^{131}I-MIBG therapy safely reduces disease burden in patients with relapsed NBL [17].

Systematic review of studies with ^{131}I-MIBG in NBL by Wilson *et al.* [18], revealed an objective tumour RR ranging from 0% to 75%. Multivariate analysis of cumulatively administered activity ([AA] measured in GBq) show that there was a positive association between response rate and cumulative AA ($p = 0.001$), but no clear relationship between response and AA/kilogram (kg; $p = 0.16$).

The primary aim of the study was feasibility/toxicity, and the secondary outcomes were: interval between chemo courses, feasibility to harvest stem cells, haematological reconstitution post ASCT and response of 2 courses of upfront ^{131}I-MIBG therapy, followed by the standard arm of the HR GPOH 2004 protocol.

2. Patients and methods

We performed a retrospective, multi-centre (Emma Children's Hospital [AMC], Amsterdam and the Erasmus MC [EMC] Sophia Children's Hospital, Rotterdam, the Netherlands), analysis of cohort pilot regimen (1/1/2005–2011), including consecutive all newly diagnosed stage 4 NBL patients, age 0–19 years, including <12 months with stage 4/M and MycN amplification (MNA) tumours, after oral informed consent from the parents [19,20]. Patients were excluded from ^{131}I-MIBG therapy if ^{123}I-MIBG uptake was insufficient, or there was a poor clinical condition (uncontrollable hypertension, orbital masses, pleural effusion). Insufficient MIBG uptake was defined as: insufficient MIBG uptake in the primary tumour and/or metastasis.

^{131}I-MIBG therapy was indicated in patients with a higher MIBG uptake level in the primary tumour than the physiological liver activity combined with MIBG uptake in known metastases, confirmed by diagnostic ^{123}I-MIBG imaging.

Data were collected from patient medical files, census date for analysis was 1/1/2012. The protocol consisted of two courses of upfront ^{131}I-MIBG therapy, followed by the standard high risk arm of the GPOH NB 2004 protocol (registered in clinical trials. gov; identifier NCT00526318). The standard arm of the HR GPOH NB 2004 protocol consists of induction chemotherapy 6 courses (alternate N5/N6 courses, interval aimed at 21 days), followed by surgery. Patients who reached complete response (CR), very good partial response (VGPR) and partial response (PR) proceeded to MAT ASCT (one mixed response (MR) patient by exemption), followed by radiotherapy to the primary tumour site and retinoic acid (Fig. 1).

The first course of ^{131}I-MIBG was aimed to start within 2 weeks from diagnosis. The scheduled interval between the two ^{131}I-MIBG courses was 4 weeks. If the platelet count was below 50×10^9/L, the second course