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A systematic review of ^{131}I-meta iodobenzylguanidine molecular radiotherapy for neuroblastoma

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Abstract The optimal use and effectiveness of ^{131}I-meta iodobenzylguanidine (^{131}I-mIBG) molecular radiotherapy for neuroblastoma remain unclear despite extensive clinical experience. This systematic review aimed to improve understanding of the current data and define uncertainties for future clinical trials. Bibliographic databases were searched for neuroblastoma and ^{131}I-mIBG. Clinical trials and non-comparative case series of ^{131}I-mIBG therapy for neuroblastoma were included. Two reviewers assessed papers for inclusion using the title and abstract with consensus achieved by discussion. Data were extracted by one reviewer and checked by a second. Studies with multiple publications were reported as a single study. The searches yielded 1216 citations, of which 51 publications reporting 30 studies met our inclusion criteria. No randomised controlled trials (RCTs) were identified. In two studies ^{131}I-mIBG had been used as induction therapy and in one study it had been used as consolidation therapy. Twenty-seven studies for relapsed and refractory disease were identified. Publication dates ranged from 1987 to 2012. Total number of patients was 1121 with study sizes ranging from 10 to 164. There was a large amount of heterogeneity between the studies with regard to patient population, treatment schedule and response assessment. Study quality was highly variable. The objective tumour response rate reported in 25 studies ranged from 0% to 75%, mean 32%. We conclude that ^{131}I-mIBG is an active treatment for neuroblastoma, but its place in the management of neuroblastoma remains unclear. Prospective randomised trials are essential to strengthen the evidence base.

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1. Introduction

Neuroblastoma is a childhood cancer with variable clinical behaviour: patients are risk stratified by age, stage and molecular pathology. Most have high-risk disease and receive intensive multi-modality therapy [1]. Systemic therapies for high-risk disease include induction chemotherapy, consolidation with myeloablative chemotherapy and minimal residual disease treatment with immunotherapy and differentiation therapy. Primary tumour treatments include surgery and radiotherapy. A poor response to induction chemotherapy identifies patients with very-high-risk disease. Five year event free survival (EFS) for high risk neuroblastoma (INSS stage 4 [2,3] is approximately 30% [4].

Most neuroblastomas express the noradrenaline transporter molecule and take up metaiodobezylguanidine (mIBG). mIBG can be radiolabelled with either ^{123}I for imaging, or ^{131}I for therapy [5]. Throughout the paper we have adhered to the conventional molecular radiotherapy terminology, where 'administered activity' (AA) refers to the amount of radioactive substance injected (measured in Bq) and 'dose' relates to the amount of radiation absorbed by the body or tumour (measured in Gy).

^{131}I-mIBG therapy, originally used for refractory or relapsed neuroblastoma, has also been incorporated into induction and consolidation treatments [5]. Haemopoietic support, typically with peripheral blood stem cells (PBSC), may be used to circumvent myelosuppression, the primary dose-limiting toxicity, to safely facilitate higher AAs. Other attempts to improve outcome include the use of concomitant chemotherapy.

The effectiveness of ^{131}I-mIBG therapy remains uncertain, and its optimal use remains undefined [5]. Our objectives were to investigate the effectiveness of ^{131}I-mIBG in the treatment of neuroblastoma, and define uncertainties to be addressed in future clinical trials, by means of a systematic review of the currently available evidence. Specific aims were to: (1) assess the activity and effectiveness of ^{131}I-mIBG therapy; (2) assess the overall quality and reliability of current evidence base; (3) identify any evidence of dose–response relationship and (4) identify any value of concomitant chemotherapy.

2. Methods

Standard systematic review methods were employed following a pre-defined protocol. MEDLINE, EMBASE and Cochrane CENTRAL bibliographic databases from inception to July 2012 were searched using terms for neuroblastoma and ^{131}I-mIBG.

Inclusion criteria were: population/setting – patients with neuroblastoma of any age and irrespective of prior therapy; intervention – ^{131}I-mIBG therapy alone or in combination with other treatments given at any time point; comparator – any accepted; design – systematic reviews, Phase I, Phase II and Phase III trials, prospective or retrospective non-comparative case series with 10 or more patients; outcomes – tumour response, overall survival (OS), event free survival (EFS), progression free survival (PFS), toxicity, adverse events, quality of life, symptom control and dosimetry. See appendix for search strategy.

Two reviewers independently assessed references for inclusion using the title and abstract with disagreements resolved by discussion. Full copies of potentially relevant papers were obtained for detailed examination. Study characteristics and results were extracted using a pre-designed data extraction form by one reviewer and independently checked by a second reviewer, with discrepancies discussed where identified. Mean cumulative AA per patient per study was calculated by summing the total AA per patient and dividing by the number of patients who were prescribed or received ^{131}I-mIBG. Six studies reported AA/kg of body weight, meaning it was not possible to calculate cumulative AA. However, these studies gave individual patient results (resulting in 18 data plots) according to AA/kg, therefore we were able to test AA against response.

In studies with multiple publications, where data differences occurred, the most recent data were utilised. Study quality was assessed using an adaption of the tool from University of York Centre for Reviews and Dissemination (York CRD) [6] with the aim to identify selection, detection and attrition bias.

Studies were assigned to one of three groups. 'Induction' studies were those where ^{131}I-mIBG therapy was used as the first line of treatment up-front in newly diagnosed patients; 'consolidation' studies were those where ^{131}I-mIBG therapy was given in conjunction with myeloablative chemotherapy after initial chemotherapy had led to a response; and 'relapsed/refractory' studies were those where ^{131}I-mIBG therapy was used in patients whose disease had progressed after an initial response to treatment, or who failed to respond well to induction chemotherapy. Ideally, we would have liked to have separated relapsed from refractory patients, but most papers put the two types of patients together and did not report outcomes separately.

Objective tumour response was defined using the International Neuroblastoma Response Criteria [2,3] as complete response (CR) or partial response (PR). Mixed response (MR), stable disease (SD) and no response (NR) did not contribute to the objective response outcome.

2.1. Statistical methods

For each study, the proportion of patients with objective tumour response with 95% confidence interval (CI) was presented. Odds ratios (ORs) with CIs were derived using logistic regression for grouped data with robust standard errors. Two covariates were included in the model: