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Different outcomes for relapsed versus refractory neuroblastoma after therapy with ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG)

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Abstract ***Background:*** ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) is a targeted radiopharmaceutical with significant activity in high-risk relapsed and chemotherapy-refractory neuroblastoma. Our primary aim was to determine if there are differences in response rates to ^{131}I-MIBG between patients with relapsed and treatment-refractory neuroblastoma.
Methods: This was a retrospective cohort analysis of 218 patients with refractory or relapsed neuroblastoma treated with ^{131}I-MIBG at UCSF between 1996 and 2014. Results were obtained by chart review and database abstraction. Baseline characteristics and response rates between relapsed patients and refractory patients were compared using Fisher exact and Wilcoxon rank sum tests, and differences in overall survival (OS) were compared using the log-rank test.
Results: The response rate (complete and partial response) to ^{131}I-MIBG-based therapies for all patients was 27%. There was no difference in response rates between relapsed and refractory patients. However, after ^{131}I-MIBG, 24% of relapsed patients had progressive disease compared to only 9% of refractory patients, and 39% of relapsed patients had stable disease compared to 59% of refractory patients ($p = 0.02$). Among all patients, the 24-month OS was 47.0% (95% confidence interval (CI) 39.9–53.9%). The 24-month OS for refractory patients

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was significantly higher at 65.3% (95% CI 51.8–75.9%), compared to 38.7% (95% CI 30.4–46.8%) for relapsed patients ($p < 0.001$).

Conclusions: Although there was no significant difference in overall response rates to ^{131}I-MIBG between patients with relapsed versusrefractory neuroblastoma, patients with prior relapse had higher rates of progressive disease and had lower 2-year overall survival after ^{131}I-MIBG compared to patients with refractory disease.

1. Introduction

Neuroblastoma is the most common extra-cranial solid tumour in children [1,2]. At diagnosis, 50% of patients have high-risk disease, due to tumour *MYCN* amplification or metastatic disease in patients older than 18 months [3]. Approximately 20% of patients with high-risk neuroblastoma progress early or are refractory to standard induction therapy, and 50% of patients who achieve remission later relapse [4,5]. Five-year overall survival (OS) for patients with high-risk neuroblastoma, even when treated with myeloablative therapy, is only 40% [4,6]. Patients with relapsed and refractory neuroblastoma have even poorer outcomes, with a 5-year OS of less than 20% [1,7].

^{131}I-metaiodobenzylguanidine (^{131}I-MIBG), a norepinephrine analogue, is a promising therapy for patients with high-risk neuroblastoma. Neuroblastoma originates in neural crest cells of the peripheral nervous system, and 90% of neuroblastomas express human norepinephrine transporter (hNET) [8,9]. When labelled with iodine-131, MIBG is a targeted radiopharmaceutical for high-risk neuroblastoma, with a response rate of 20–40% in early phase studies and a recent meta-analysis [10–15]. However, it is not well established if patients with relapsed disease respond differently to ^{131}I-MIBG compared to patients with refractory disease.

Our primary aim was to investigate whether there are differences in overall response (OR) to ^{131}I-MIBG alone or combined with other agents, between relapsed and refractory neuroblastoma. Our secondary aims were to compare baseline clinical characteristics in these two cohorts as well as OS after therapy with ^{131}I-MIBG.

2. Patients and methods

2.1. Study design

This was a retrospective cohort analysis of 218 patients with relapsed or refractory neuroblastoma treated with ^{131}I-MIBG at UCSF Benioff Children's Hospital on three local and six New Approaches to Neuroblastoma Therapy (NANT) clinical trials between 30st August 1996, and 23st April 2014 (Supplementary Table 1). Results were obtained by chart review and database abstraction.

^{131}I-MIBG treatment protocols were approved by the UCSF institutional review board (IRB), and informed consent was obtained for all patients. The UCSF IRB approved this retrospective analysis.

2.2. Patient eligibility and treatment

Patients aged >1 year with high-risk neuroblastoma treated on nine protocols (Supplementary Table 1) were eligible for this study. Of these patients, 154 have been included in primary trial publications [14–22], and 64 have not.

Patients were required to have MIBG-avid disease within 4–6 weeks before enrolment and to have failed to achieve a partial response (PR) to induction therapy, or have relapsed or progressive disease. Patients enroled in NANT 1999–1901, NANT 2001–2002, NANT 2004–2006, NANT 2007–2003 and ^{131}I-MIBG Vincristine/Irinotecan, were also eligible if they had PR but persistent active disease. Prior therapy must not have included ^{131}I-MIBG but could include chemotherapy, surgical resection, radiation and autologous stem cell transplant (ASCT) (except NANT 1999–01 and 2001–2002, which excluded prior ASCT).

Patients received 6.3–20.9 mCi/kg (233–773 MBq/kg) of ^{131}I-MIBG, except for patients treated on NANT 2000–2001, a double infusion protocol where patients received up to 50.1 mCi/kg (1854 MBq/kg) over two treatments at a two-week interval. ^{131}I-MIBG intended dose levels were stratified into three categories for this analysis: a low dose of $\leqslant$12 mCi/kg ($\leqslant$444 MBq/kg), an intermediate dose of >12 to <18 (<666 MBq/kg) and a high dose of $\geqslant$18 mCi/kg. In the analysis, 13 mCi/kg (481 MBq/kg) was used as the lower threshold and 17 mCi/kg (629 MBq/kg) was used as the higher threshold to account for dosing variation.

2.3. Primary predictor variable

Patients were grouped by their response to prior therapy. Relapsed patients had disease recurrence or progression at any time prior to study enrolment. This included patients who achieved complete response (CR) or PR to prior induction therapy and then progressed, and patients who progressed without achieving CR or PR. Refractory patients included those who had

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