Survival in patients with High-Risk Neuroblastoma without autologous stem cell transplant and dinutuximab

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Abstract

Background: The majority of patients with high-risk neuroblastoma (HR-NB) in low- and middle-income countries (LMIC) do not have access to autologous stem cell transplant (ASCT) and dinutuximab. Consolidation with non-myeloablative chemotherapy is not well-defined, and the outcomes are variable. We report a single-center outcome of patients with HR-NB, treated with non-myeloablative consolidation. A tabulated compilation of similar reports is included. Procedure: A retrospective chart review of patients with HR-NB was performed from January 2009 till June 2016. Patients were treated on the backbone of HR-NBL1/SIOPEN protocol. Treatment included induction with rapid-COJEC, surgery, consolidation, radiotherapy to the primary tumor, and differentiation therapy with isotretinoin. Consolidation included 4 cycles of topotecan, vincristine, and doxorubicin (TVD) instead of ASCT. Infusion of vincristine and doxorubicin were modified for ease and to enable administration in daycare. Results: Over 7-$\frac{1}{2}$ years, 28 patients with HR-NB were treated. Two (7%) patients had therapy-related mortality. A relapse or disease progression occurred in 11 (39%) patients at a median duration of 17 months (IQR: 5, 18). Treatment abandonment was observed in 4 (14%) patients. The 4-year event-free survival was 29.3%. The median follow up of disease-free patients is 49 months (IQR: 45, 79). Patients with relapse were not treated further. Conclusions: A 4-year EFS of 29.3% was observed when 4-cycles of TVD were administered instead of ASCT in patients with HR-NB. The study and the review will aid stakeholders in LMIC for decision-making while considering the options of treatment for HR-NB if access to ACST and dinutuximab is lacking.

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Conclusions: A 4-year EFS of 29.3% was observed when 4-cycles of TVD were administered instead of ASCT in patients with HR-NB. The study and the review will aid stakeholders in LMIC for decision-making while considering the options of treatment for HR-NB if access to ACST and dinutuximab is lacking.

Introduction

High-risk neuroblastoma (HR-NB) is a challenging disease to treat. The state of the art treatment of HR-NB includes induction chemotherapy, surgery, consolidation with autologous stem cell transplantation (ASCT), radiotherapy, immunotherapy with dinutuximab, and differentiation therapy with isotretinoin. The role of tandem ASCT is being explored.[1] The survival rates in trials from high-income countries (HIC) are between 40-60%.[2-4]

There is limited data on the outcome of HR-NB from low-middle income countries (LMIC), likely reflecting a publication bias of the disease with an unfavorable outcome. The typical challenges in LMIC include sub-optimal supportive care, finances, availability of beds, undernutrition, and treatment abandonment.[5] The aid from non-government organizations is frequently directed to cancers with a favorable outcome. Expertise and facility for high-dose chemotherapy with ASCT rescue is available in limited centers in LMIC.[6-9] Dinutuximab is not available in the majority of LMIC, including India. A diagnosis of HR-NB is grueling for the pediatric oncology team, the patient, and the family alike. Amid the arduous situation, the treating physician is faced with the question if attempting a cure of HR-NB without ASCT and dinutuximab is worthwhile.

In the absence of ASCT, therapy may be consolidated with non-myeloablative chemotherapy. Limited standardized protocols for effective chemotherapy consolidation are reported.[10]The survival of HR-NB with ASCT and low-cost adaptations for performing ASCT have been published from our center recently.[7]Along the road to developing ASCT services, several patients in our center were unable to opt for ASCT, due to the constraints listed earlier. They were treated with HR-NBL1/SIOPEN protocol without ASCT. Consolidation with ASCT was replaced with 4 cycles of topotecan, vincristine, and doxorubicin (TVD). The outcome of patients with HR-NB treated without ACST and dinutuximab is reported in this manuscript.

Methods

A retrospective chart review of patients with HR-NB was performed from January 2009 till June 2016 (7$\frac{1}{2}$-years). Approval was obtained from the institute's ethics committee. High-risk disease was defined as, a) stage 4 disease in children older than 18-months, b) stage 4 disease, age 12-18 months, with unfavorable histology, or, c) any age, stage 3 or 4 disease, MYCN amplified.[10] Any patient with stage 3 disease in whom MYCN amplification was not available was excluded from the analysis due to uncertainty in risk categorization.

Imaging consisted of either computed tomography or magnetic resonance imaging of the primary site. The diagnosis was by fine-needle aspiration cytology or biopsy of the primary tumor.[11] Bilateral bone marrow aspirate and trephine were performed in all. Technetium-99m bone scintigraphy was done until April 2012. Subsequently, a positron emission tomography scan was performed to stage the disease. Weight for age was derived from WHO Anthro software v3.2.2 and Anthro plus software v1.0.4 for patients below 5-years, and 5-10 years, respectively.[12,13] A value between - 2 and - 3 Z score was classified as moderate, and below - 3 Z score as severe under-weight.[14]

2.1 Treatment details

The treatment algorithm is illustrated in Figure 1. The induction was with rapid COJEC as per the HR-NBL1/SIOPEN protocol.[15]The drugs in rapid COJEC included cisplatin, vincristine, carboplatin, etoposide, and cyclophosphamide. Each cycle was administered at 10 days interval, irrespective of count recovery. Granulocyte-colony stimulating factor (G-CSF) was administered prophylactically after every cycle. A reassessment was performed at the end of induction chemotherapy. As per the international neuroblastoma response criteria, the response was categorized as complete (CR), very good partial (VGPR), partial (PR), mixed (MR), no response (NR), or progressive disease (PD) at primary and metastatic sites.[16] A favorable reassessment was followed by surgical resection of the primary tumor. Consolidation was with 4 cycles of TVD (Table 1). Each cycle of TVD was supported with G-CSF. The subsequent cycle was administered at 21-28 days following count recovery. TVD was administered either as in-patient or outpatient, subject to the availability of beds. Infusion of vincristine and doxorubicin was modified for ease and to enable administration in daycare. Vincristine was administered as an intravenous push on days 5 and 6 instead of continuous 48-hours infusion recommended in the SIOPEN protocol. Doxorubicin was administered as a 4-hours infusion on days 5 and 6 instead of a continuous 48-hours infusion. Consolidation chemotherapy was followed by external beam radiotherapy to the tumor bed, and differentiation therapy with six, 2-weekly cycles of isotretinoin. No further therapy was offered to patients who had a relapse or progressive disease.

2.2 Statistical analysis

Survival was determined from the beginning of induction chemotherapy by the Kaplan-Meier method. An event was defined as abandonment, relapse, or death from any cause. Patients who were lost to follow up after completion of therapy were censored at the point of the last contact. Statistical analysis was performed using SPSS statistical package v23.0 (SPSS Inc., Chicago, IL). P-value was two-sided, and a value of < 0.05 was considered significant.

Results

During the study period of $7\frac{1}{2}$ years, 184 new patients with neuroblastoma were diagnosed. The risk stratification was available for 150 (82%) patients. The disease was stratified as high-risk: 105 (70%), intermediate-risk: 17 (11%), low-risk: 20 (13%), or as very low-risk: 8 (5%). Parents/guardians of 51 (48%) children with high-risk disease did not opt for curative therapy. The reasons for refusal included a) financial constraints, b) dissuaded by the poor prognosis, and, c) inability to reside in the vicinity of the hospital for the duration of the lengthy therapy. Twenty-six (25%) patients were treated with ASCT, results of which have been reported earlier.[6]Twenty-eight (27%) patients were treated on a non-ASCT protocol with TVD consolidation. The management and survival of the 28 patients who received non-ASCT based therapy are detailed in this manuscript. The patient characteristics are listed in Table 2.

3.1 Treatment

The flowchart of treatment administered, and the outcome is illustrated in Figure 2. Rapid COJEC was administered over a median duration of 91 days (IQR: 83.5, 96). The 28 patients received 219 cycles of rapid COJEC. Episodes of febrile neutropenia were recorded in 18 (8%) cycles, resulting in a single (3.6%) mortality. The response was assessed following rapid COJEC in 25 patients. Remission was observed in 21 (84%) patients, with CR in nil, VGPR in 4, and PR in 17 patients. Four (16%) patients did not achieve remission with MR and PD in 2 each.

Surgery was performed in 18 (72%) patients, including debulking in 11 (61%) and a complete resection in 7 (39%). In 7 patients, surgery was not performed due to a) progressive disease at metastatic sites (n=2), b) lack of remission in bone marrow (n=2), c) reduction in the size of the primary tumor to a small size deemed futile for surgical resection (n=2) or, d) treatment abandonment (n=1). Seventy-two cycles of TVD were administered to 20 patients. Thirty-three (46%) episodes of febrile neutropenia occurred during the administration of TVD, with a single (5%) mortality. Radiotherapy to the primary tumor, followed by six, 2-weekly cycles of isotretinoin were administered to 17 patients.

3.2 Survival

A relapse or progressive disease was noted in 11 (39%) patients at a median duration of 17 months (IQR: 5, 18). Following the completion of therapy, 2 (7%) patients died at home at 21 and 31 months of follow up. The cause of death could not be ascertained. Two patients discontinued follow up at 12 and 21 months; they were non-contactable and were censored at the point of the last contact. Nine patients are alive at a median duration of 49 months (IQR: 45, 79). Two (50%) patients who had a VGPR and 7 (41%) patients with PR are alive. No patient who had MR or PD survived. Of the 9 patients who are alive, surgery was performed in all except one, in whom the primary, following rapid COJEC, had reduced to size, considered too small for resection. The extent of surgical resection in survivors was complete in 2, and debulking in 6. The 4-year overall survival (OS), as well as event-free survival (EFS) of patients (n=28), was 29.3% (Fig. 3).

4. Discussion

Myeloablative chemotherapy followed by ASCT, and immunotherapy with dinutuximab are established modalities in the current treatment for HR-NB.[2] The role of sequential transplants is being investigated. A recent Children's Oncology Group trial demonstrated a 3-year EFS of 61.6% with tandem transplants, including thiotepa followed by dose reduced carboplatin, etoposide, and melphalan.[1] The strategy of treating patients without ASCT has been reported in a single-center trial by Kushner et al.[17] While an impressive 5-year EFS of 51% was observed without ASCT, the protocol included anti-GD2 antibody besides multiagent intensive chemotherapy.[17]

The majority of children with HR-NB reside in LMIC, where ASCT, as well as dinutuximab, are unavailable to most. In centers where facilities for ASCT are available, expense and waiting period, along with diverse resource allocation, may render it difficult to offer ASCT to every patient with HR-NB. Turkish Pediatric Oncology Group reported a median waiting period of 8 months (range: 5-16) for proceeding to ASCT from diagnosis.[8] ASCT was administered to merely 17% of patients in the study from Turkey.[8] Further, the time lag resulted in disease progression in 9%. Among 295 patients with HR-NB in the National data from South Africa, merely 11 (3.7%) received ASCT due to limited availability and dependence on private insurance.[18] Similarly, 8.8% of patients with stage 4 neuroblastoma were consolidated with ASCT in a single-center report from New Delhi, India.[19] Selected reports on the survival of HR-NB without ASCT and dinutuximab are summarized in Table 3. The survival is wide-ranging, with the majority of data indicating an EFS below 20%.

Alternative strategies to consolidation with ASCT have been explored in settings with limited resources. The Pediatric Oncology in Developing Countries committee of the International Society of Pediatric Oncology (SIOP-PODC) has published guidelines for the management of neuroblastoma in LMIC.[10] Multiple chemotherapy options in place of ASCT are suggested with curative intent. The options include, a) 4 cycles of modified Pediatric Oncology Group (POG) 9341 regimen, consisting of etoposide, ifosfamide, cisplatin, carboplatin, vincristine and doxorubicin in varying combinations, b) 2 cycles each of cyclophosphamide, doxorubicin, vincristine (CAdO) and carboplatin, etoposide (CE) regimens, or c) 6-cycles of cyclophosphamide and topotecan.[10] The continuation of 4-cycles of POG 9341 has an expected EFS of 20%.[3,10] Oral cyclophosphamide has been used for maintenance therapy as well. It is administered for 4 cycles, 8 days each at 150 mg/m^2 per day, with a 3-year EFS of 31%.[29]

Topotecan has been utilized in the treatment of HR-NB in several trials. In the HR-NBL1/SIOPEN trial, 2-cycles of TVD were administered to patients who had an inadequate response to induction chemotherapy, preventing progression to ASCT. The administration of TVD enabled 36% additional patients to achieve a PR status, mandated for ASCT.[30] However, the EFS was reduced to 24% in comparison to 42% in patients who did not require TVD (P-value 0.0036).[2] Administration of TVD is no longer recommended in the CCLG guidelines for patients who fail to achieve metastatic clearance due to a lack of evidence showing improvement in survival.[2, 31]

Topotecan has been administered infrequently in newly diagnosed HR-NB. In a pilot study by COG, pharmacokinetically guided doses of topotecan were administered along with cyclophosphamide. An induction response rate of 84% was observed.[32] A similar combination was used in a multicentric trial in Thailand, with

82% of patients attaining remission.[33] A phase II investigational window study by POG noted an objective response (complete, partial or mixed) with 2-cycles of single-agent topotecan.[34]

Lacking access to ASCT in the selected cases of HR-NB, we choose to administer 4-cycles of TVD as consolidation instead. Multiple cycles, ranging from 1-9 of TVD, were administered in phase II multicentric Italian study in children with relapsed or refractory neuroblastoma.[35] Progression-free survival was observed in 15 (60%) children at a median of 9 months.[35] We observed mortality of 3.5% and 5% during induction and consolidation, respectively. Mortality of 4.1% was reported with rapid COJEC in 130 children by European Neuroblastoma Study Group and the Children's Cancer and Leukaemia Group in 2008.[36] As per SIOP-PODC, a toxic death rate exceeding 5% for induction and 10% for consolidation should prompt an assessment and reduction of treatment intensity if supportive care cannot be augmented.[10] HR-NBL1/SIOPEN trial did not report toxic deaths during rapid COJEC as well as with 2-cycles of TVD.[30] Morbidity with TVD was predominantly hematological with grade 3 or 4 neutropenia in 84% patients.[30] Admission for the administration of antibiotics was recorded in 34.1% cycles.[30] Admission for antibiotics was observed in 46% cycles of TVD in our study. We consider toxicity from rapid COJEC and TVD in our setting to be acceptable.

For ASCT to be widely available to patients with HR-NB in LMIC, we incorporated several low-cost adaptations, reported earlier.[7] The strategy now enables us to offer ASCT universally to all patients with HR-NB in our center. The 3-year OS of patients with HR-NB with ASCT was 41% in our center. The OS with ASCT exceeds the OS of 29.3% observed without ASCT in the current study, though the difference is not significant (P-value 0.46). The efficacy of ASCT for HR-NB cannot be suitably commented on the comparison of the two studies, due to the limited size of cohorts. The limitations of the study are a retrospective design with a limited number of patients from a single-center.

In conclusion, a 4-year EFS of 29.3% was observed when 4-cycles of TVD were administered instead of ASCT in patients with HR-NB. The study will aid stakeholders in LMIC for making informed decisions while considering the options of treatment for HR-NB if access to ACST and dinutuximab is lacking.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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LEGENDS

FIGURE 1 Treatment algorithm of patients with high-risk neuroblastoma. COJEC, cisplatin, vincristine, carboplatin, etoposide, cyclophosphamide; TVD, topotecan, vincristine, doxorubicin.

FIGURE 2 Flowchart illustrating treatment administered and the outcome of 28 patients with high-risk neuroblastoma. ASCT, autologous stem cell transplantation; BM, bone marrow; COJEC, cisplatin, vincristine, carboplatin, etoposide, cyclophosphamide; FN, febrile neutropenia; IQR, interquartile range; TVD, topotecan, vincristine, doxorubicin.

FIGURE 3 Survival of patients with high-risk neuroblastoma (n=28). Overall and event-free survival is similar (29.3%), as no patient with relapse was treated.

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`Table 1. TVD protocol. 2 July 2020.docx` available at https://authorea.com/users/319917/articles/470873-survival-in-patients-with-high-risk-neuroblastoma-without-autologous-stem-cell-transplant-and-dinutuximab

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`Table 2 Patient characteristics 2 July 2020.docx` available at https://authorea.com/users/319917/articles/470873-survival-in-patients-with-high-risk-neuroblastoma-without-autologous-stem-cell-transplant-and-dinutuximab

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`Table 3. Outcome for HR NB. 19 July 6.35 pm.docx` available at https://authorea.com/users/319917/articles/470873-survival-in-patients-with-high-risk-neuroblastoma-without-autologous-stem-cell-transplant-and-dinutuximab