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Survival of high-risk pediatric neuroblastoma patients in a developing country

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Abstract

Little information is available about survival of high-risk pediatric neuroblastoma patients in developing countries. We aimed to assess survival among high-risk pediatric neuroblastoma patients in La Plata, Argentina. Individuals eligible for our cohort were aged <20 years when diagnosed with high-risk neuroblastoma and received cancer-directed therapy including stem cell transplantation at Hospital de Niños Sor Maria Ludovica between February 1999 and February 2015. We estimated overall survival probabilities using an extended Kaplan-Meier approach. Our study population comprised 39 high-risk neuroblastoma patients, of whom 39% were aged >4 years at diagnosis, 54% were male, and 62% had adrenal neuroblastoma. We observed 18 deaths, and the median survival time of our study population was 1.7 years. The 5-year overall survival probability was 24% (95% confidence limits [CL]: 10%, 41%). In contrast, 5-year survival of high-risk neuroblastoma patients ranges between 23% and 76% in developed countries. Survival among high-risk neuroblastoma patients is generally poor regardless of geographic location, but our results illustrate dramatically worse survival for patients in a developing country. We speculate that the observed survival differences could be attenuated or eliminated with improvements in treatment and supportive care, but addressing these issues will require creative solutions because of resource limitations.

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CONFLICT OF INTEREST

The authors declare no financial or non-financial conflicts of interest.

AUTHOR CONTRIBUTIONS

JCE contributed to data analysis, interpretation of results, and drafted the manuscript. SG contributed to data collection and interpretation of results. PHA contributed to data analysis and interpretation of the results. JMC contributed to data analysis. ABF contributed to data collection CR contributed to data collection. RPO developed the study design, and contributed to data analysis and interpretation of results. All authors contributed to critical revision of the manuscript and approved the final version.

Keywords

neuroblastoma; stem cell transplantation; mortality; disparity; developing country

INTRODUCTION

Low- and intermediate-risk neuroblastoma, characterized by favorable stages and age <1 year at time of diagnosis, have 5-year overall survival >90% following chemotherapy and surgical resection. In contrast, 5-year overall survival for high-risk neuroblastoma, characterized by features such as metastasis, age >1 year, and amplified *MYCN* oncogene, is only 40 – 50% despite intensive treatment protocols that include chemotherapy, surgery, radiation, and stem cell transplantation.(1, 2) The current evidence about survival among high-risk neuroblastoma patients is almost exclusively derived from cohorts in developed countries. Nevertheless, the burden of pediatric neuroblastoma is nearly as high in developing countries such as Argentina as in developed countries such as the United States (age-standardized incidence=7.9(3) and 10 per million children,(4) respectively). Evidence from developing countries may help identify survival disparities among high-risk pediatric neuroblastoma patients compared with developed countries. Therefore, we aimed to describe survival among high-risk pediatric neuroblastoma patients in Argentina and compare survival between our setting and other settings.

METHODS

Study population

Hospital de Niños Sor Maria Ludovica in La Plata, Argentina is a public institution that serves patients regardless of insurance status. The pediatric oncology unit of the hospital includes 17 beds for inpatient care of children with hematologic malignancies and solid tumors. In addition to serving the local catchment area, Hospital de Niños Sor Maria Ludovica is a referral center for high-risk pediatric neuroblastoma patients from hospitals in Argentina and neighboring countries.

Individuals eligible for our cohort were aged <20 years when diagnosed with high-risk neuroblastoma and received cancer-directed therapy including stem cell transplantation at Hospital de Niños Sor Maria Ludovica in La Plata, Argentina between February 1999 and February 2015. Consistent with national guidelines in Argentina, high-risk neuroblastoma was defined as meeting one of the following criteria: 1) age ≥1 year and disseminated disease (stage 4 of International Neuroblastoma Staging System [INSS] or stage M of International Neuroblastoma Risk Group Staging System [INRGSS]); 2) stages 2 or 3 (INSS) or L1, L2, or MS (INRGSS) with *MYCN* amplification, or 3) age <1 year with *MYCN* amplification. High-risk neuroblastoma patients were treated according to modified N7(5) or European SIOP Neuroblastoma (SIOPEN HR-NBL1(6)) protocols. The induction therapy backbone included cyclophosphamide, doxorubicin, and vincristine (courses 1,2, and 4), and cisplatin and etoposide (courses 3 and 5). Consolidation therapy involved administration of busulfan (p.o. 4 times per day) and melphalan, with 13-cis retinoic acid administered following autologous stem cell transplantation. Supportive care included

prophylaxis with acyclovir and trimethoprim-sulfamethoxazole. The treatment approach remained largely unchanged throughout the study period. This study was considered exempt from institutional review board oversight.

Variables

Medical records containing prospectively documented patient information from time of neuroblastoma diagnosis were abstracted using a standardized data collection form. Baseline information included demographic and clinical characteristics such as neuroblastoma diagnosis and location of primary tumor. We defined malnourishment as a weight for age z-score <−2 using the World Health Organization reference population.(7) Resource limitations in this setting precluded systematic assessments of prognostic factors such as DNA ploidy, *MYCN* gene amplifications, 1p36 deletions, and serum biomarkers. Follow-up information included basic data about the stem cell transplantation procedure and mortality.

Data analysis

Prior studies of survival among high-risk pediatric neuroblastoma patients used inconsistent measures of survival duration. Some studies measured survival since the time of neuroblastoma diagnosis and others measured survival since the time of stem cell transplantation. Unfortunately, neither of these approaches properly accounted for the time between diagnosis and transplantation, which can result in biased survival probabilities (8) if the goal is to estimate survival after transplantation. Consequently, we used an extended Kaplan-Meier approach for estimating survival probabilities.(8) We used age as the time-scale,(9) where person-time was observed from the age of neuroblastoma diagnosis, but entry into the cohort did not occur until the age at transplantation (i.e. delayed entry). For comparative purposes, we also estimated overall survival probabilities using the age of neuroblastoma diagnosis and the age of transplantation, respectively. Patients contributed follow-up time until death, loss to follow-up, or end of the study period (May 1, 2015).

Comparison of survival with other populations

We systematically searched PubMed/Medline for published reports regarding overall survival among high-risk pediatric neuroblastoma patients who underwent autologous stem cell transplantation. We used combinations of the search terms: pediatric OR paediatric OR child; neuroblastoma; high-risk OR advanced; and overall survival. Eligible reports were published between 2000 and 2016, and reported 5-year overall survival probabilities. Reviews, editorials, commentaries, and phase 1 or phase 2 randomized controlled trials (because of limited follow-up in such studies) were excluded. We abstracted information pertaining to each study, including publication year, study period, region, sample size, consolidation therapy, the measure of survival duration (time since diagnosis or transplantation), and 5-year overall survival probabilities specific to high-risk pediatric neuroblastoma patients who underwent autologous stem cell transplantation.

We estimated 5-year survival differences, which individually compared the 5-year overall survival probabilities reported in eligible studies with the 5-year overall survival probability observed in our study. To estimate 95% confidence limits (CL) for the survival difference, we first estimated the standard errors (SE) for 5-year overall survival probabilities based on

the reported 95% CL from eligible studies, where SE = (upper limit of CL – lower limit of CL)/3.92.

These standard errors were then used to compute standard errors for the survival difference (SE_{SD}) as follows(10):

$$SE_{SD}=(SE_A{}^2+SE_B{}^2)^{1/2}$$

where SE_A was the standard error of the reported 5-year survival probability and SE_B was the standard error of 5-year survival probability observed in our study. The corresponding 95% CL were then computed as: point estimate for survival difference ± 1.96*SE_{SD}.

RESULTS

The eligible population comprised 40 high-risk pediatric neuroblastoma patients, but incomplete information for one patient resulted in a study population of 39 patients. Table 1 summarizes the characteristics of our study population. Briefly, the majority of patients (56%) were transplanted between 2000 and 2007. Patients were primarily aged ≤4 years (61%) at diagnosis and the majority were males (54%). The most common site of neuroblastoma was the adrenal gland (62%). The prevalence of malnourishment was low (2.6%) for patients with available evaluable data (average prevalence for hospitalized patients in Argentina is 12% (11)). The median follow-up for surviving patients was 1.7 years (interquartile range = 1.2 – 7.9).

Figure 1 illustrates the survival curves for our study population based on approaches used in prior studies and the approach that accounts for time to transplantation. We observed 18 observed deaths, of which 15 were attributable to disease progression, 1 was attributable to pulmonary aspergillosis, 1 was attributable to engraftment failure, and 1 was attributable to sepsis. The median survival for this cohort was 1.7 years and the 5-year overall survival probability was 24% (95% CL: 10%, 41%) when accounting for time to transplant. The median survival was 2.4 years and 0.74 years if age at neuroblastoma diagnosis and age at transplant, respectively, were designated as the start of observation.

Table 2 describes 13 published reports,(12–24) and the current study, of 5-year overall survival among high-risk pediatric neuroblastoma and summarizes survival differences compared with our population. Half of the reports pertained to high-risk pediatric neuroblastoma cohorts in North America. The median sample size was 43 (interquartile range=26 – 89). Consolidation regimens were heterogeneous across studies, but 57% included either total body or localized radiation. Survival duration was measured as time since transplantation in 46% of studies. Except for one study,(24) the 5-year overall survival estimate in our population was lower than other populations, with the largest 5-year absolute survival difference being 52% (95% CL: 33%, 71%).

DISCUSSION

We analyzed data from 39 patients observed over 16 years in La Plata, Argentina to address a gap in the literature about survival of high-risk pediatric neuroblastoma patients treated with stem cell transplantation in developing countries. Our results suggest markedly worse survival in this setting compared with high-risk pediatric neuroblastoma patients in North America, Europe, and Asia. Specifically, 5-year overall survival in our setting was 24% (95% CL: 10%, 41), whereas the highest reported 5-year overall survival in North America was 76% (95% CL: 66%, 88%) in a highly select group of high-risk pediatric neuroblastoma patients.(12) In addition, our review of prior studies suggests considerable variation in survival even between developed countries. Nevertheless, several issues warrant consideration when interpreting the survival estimate for our population and the survival differences that compare our estimates with published estimates.

Our overall survival estimate may be sensitive to bias from diverse mechanisms. For example, neuroblastoma may be underdiagnosed in developing countries.(25) If children with high-risk pediatric neuroblastoma, who would have been eligible for inclusion in our study, died before being diagnosed and these children had a rapid course of disease, then the survival probabilities in our study may be overestimated. Even if neuroblastoma were diagnosed, the standard criteria for high-risk neuroblastoma evolved over the course of our study period. Although all patients in our study population met current criteria, certain neuroblastoma patients might have been high-risk but unidentified, particularly considering the lack of systematic cytogenetic assessment in our setting. We speculate that if any high-risk neuroblastoma patients were excluded from our study population, our survival probabilities are overestimated because survival of unidentified but eligible high-risk patients would have been poor without appropriate therapy. Lastly, similar to other studies of pediatric cancer populations in developing countries,(26) loss to follow-up was common in our study. Loss to follow-up was censored in our analysis, but the evidence does not suggest that patients would have survived without completing therapy. Consequently, this mechanism of bias would also result in overestimated survival probabilities in our study.

The estimated 5-year survival differences between our setting and other settings may be largely attributable to differences in treatment protocols and supportive care.(26, 27) The 5-year survival difference was greatly attenuated (4.2%, 95% CL: −25%, 33%; 11%, 95% CL: −8.1%, 30%) when our setting was compared with settings that used a similar consolidation regimen.(15, 17) In addition, treatment delays, host prognostic factors, and environmental factors may contribute to variation in survival between settings.(26, 28)

In summary, survival among high-risk neuroblastoma patients is generally poor regardless of geographic location, but our results illustrate dramatically worse survival for high-risk neuroblastoma patients in a developing country. We speculate that the observed survival differences could be attenuated or eliminated with improvements in treatment and supportive care, but addressing these issues will require creative solutions because of resource limitations. These resource limitations may be addressed with a focus on capacity building through collaborative efforts.(28) For example, twinning programs, which are based on partnering and interaction between hospitals in developing countries and cancer centers in

developed countries, have improved survival and outcomes for pediatric cancer patients in developing countries.(29, 30) Despite the success of twinning programs, this approach has not been specifically applied in the context of high-risk neuroblastoma. Future studies are needed to assess the effectiveness of twinning programs and other approaches for improving survival among high-risk neuroblastoma patients in developing countries.

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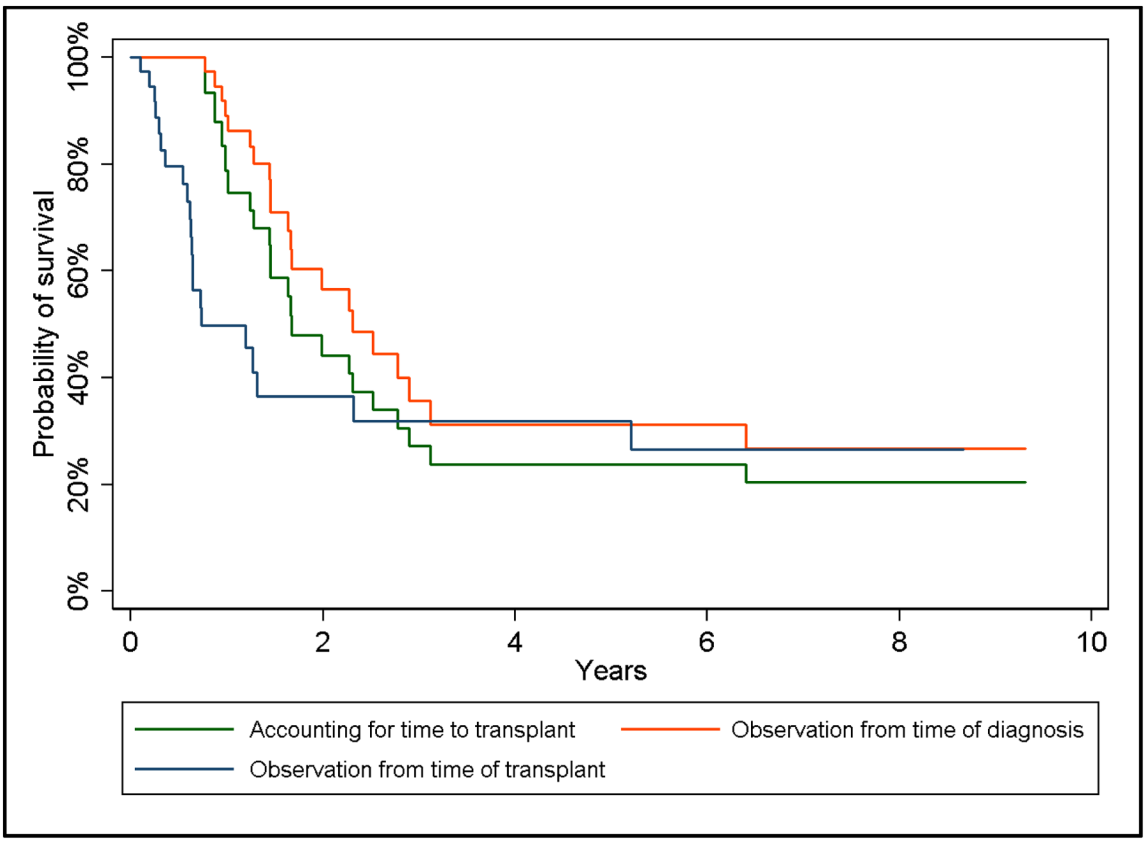

Figure 1.
Survival curves for high-risk pediatric neuroblastoma patients in La Plata, Argentina based on the measure of survival duration.

Table 1

Characteristics of high-risk pediatric neuroblastoma patients treated in La Plata, Argentina between February 1999 and February 2015.

Characteristic	***n* (%)**
Transplant period	
2000 – 2007	22 (56)
2008 – 2015	17 (44)
Age at diagnosis	
>4 years	15 (39)
≤4 years	24(61)
Age at transplantation	
>4 years	23 (59)
≤4 years	16 (41)
Sex	
Male	21 (54)
Female	18 (46)
Site of primary tumor	
Adrenal	24 (62)
Retroperitoneal	7 (18)
Mediastinal	3 (7.7)
Other	5 (13)
Malnourished[a]	
Yes	1 (2.6)
No	29 (97)
Vital status at end of study	
Alive	21 (46)
Deceased	18 (54)

[a]Malnourished status based on weight-for-age z-score at the time of transplantation and the World Health Organization reference standard. Unreliable or missing data precluded z-score estimation for 9 patients.

Table 2

Comparison of 5-year overall survival in studies of high-risk pediatric neuroblastoma patients treated with autologous stem cell transplantation.

Study (year)	Study period	Region	Sample size	Consolidation regimen	Survival duration	5-year survival (95% CL)	5-year survival difference (95% CL)
Kushner et al. (2015) (12)	2003 – 2013	North America	60	Localized radiation, 3F8, isotretinoin	Time since transplantation	76% (66%, 88%)	52% (33%, 71%)
Englum et al. (2015) (13)	1990 – 2012	North America	87	Total body irradiation, carboplatin, etoposide, cyclophosphamide, melphalan	Time since diagnosis	47% (37%, 59%)	23% (3.9%, 42%)
Mazloom et al. (2014) (14)	2006 – 2011	North America	30	Localized radiation, carboplatin, etoposide, melphalan	Time since diagnosis	59% (45%, 78%)	35% (12%, 58%)
Tan et al. (2012) (15)	1987 – 2008	Asia	18	Localized radiation, busulfan, melphalan	Time since diagnosis	28% (4.0%, 53%)	4.2% (−25%, 33%)
Granger et al. (2012) (16)	1998 – 2000	North America	22	Localized radiation, carboplatin, etoposide, cyclophosphamide, thiotepa	Time since transplantation	46% (35%, 57%)	22% (2.9%, 41%)
Monnereau-Laborde et al (2011) (17)	1995 – 1996	Europe	20	Busulfan, melphalan	Time since diagnosis	35% (24%, 46%)	11% (−8.1%, 30%)
Matthay et al. (2009) (18)	1991 – 1996	North America	189	Total body irradiation, carboplatin, etoposide, melphalan	Time since transplantation	39% (35%, 43%)	15% (−1.2%, 32%)
Trahair et al. (2007) (19)	1985 – 2003	Australia	40	Total body irradiation, cisplatin, teniposide, adriamycin, melphalan; thiotepa, etoposide, cyclophosphamide; carboplatin, etoposide, melphalan	Time since diagnosis	60% (52%, 68%)	36% (18%, 54%)
Kim et al. (2007) (20)	1996 – 2004	Asia	46	Carboplatinum, etoposide, melphalan; carboplatin, topotecan, thiotepa; etoposide, melphalan; carboplatin, topotecan, melphalan	Time since transplantation	69% (60%, 78%)	45% (27%, 93%)
George et al. (2006) (21)	1994 – 2002	North America	89	Total body irradiation, carboplatin, etoposide, melphalan, cyclophosphamide	Time since diagnosis or transplantation	62% (51%, 72%)	38% (19%, 57%)
Pritchard et al. (2005) (22)	1982 – 1985	Europe	90	Melphalan	Time since transplantation	47% (30%, 64%)	23% (−0.05%, 46%)
Berthold et al. (2005) (23)	1997 – 2002	Europe	295	Carboplatin, etoposide, melphalan	Time since diagnosis	45% (39%, 52%)	21% (4.1%, 38%)
Klaassen et al. (2003)[a] (24)	1989 – 1995	North America	26	Cyclophosphamide, carboplatinum, etoposide; cyclophosphamide, carboplatin, melphalan	Time since diagnosis	23%[b]	−1%**
Current	2000 – 2015	South America	39	Busulfan, melphalan	Time since transplantation accounting for time since diagnosis	24% (10%, 41%)	Reference

[a] Presented results pertain to stage 4 neuroblastoma

[b] Inadequate data reported to estimate confidence limits