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Late Effects in Survivors of Tandem Peripheral Blood Stem Cell Transplant for High-Risk Neuroblastoma

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Abstract

Background—Increasing numbers of children with advanced neuroblastoma are achieving cure. We describe the clinical late effects specific to survivors of stage IV neuroblastoma all similarly treated using tandem autologous peripheral blood stem cell rescue with TBI.

Method—The medical records of 35 neuroblastoma patients treated at CHOP between 1997 and 2001 were examined. Eighteen of the 35 patients died of progressive disease, and 4 were lost to follow-up. Thirteen patients continue to follow-up in our Multi-disciplinary Cancer Survivorship Clinic where they are evaluated and monitored by a consistent group of subspecialists that evaluate long-term sequelae. Data on treatment exposures including TBI and treatment related sequelae identified by clinician assessment and/or diagnostic testing were collected.

Results—Results indicate late effects were present in all 13 subjects, 12 of whom suffered from multiple negative sequelae, including issues with growth hormone deficiency, dental problems, osteochondromas and hearing deficiencies, among others, most at higher rates than reported previously.

Conclusions—The findings in this small cohort indicate the need for future prospective studies of this intensive pediatric cancer treatment, and underscore the importance of medical intervention and long-term monitoring of these at-risk subjects to increase overall quality-of-life.

Keywords

cancer survivorship; late effects; neuroblastoma

INTRODUCTION

Neuroblastoma is the second most commonly occurring solid tumor in pediatric patients [1]. Although some progress has been made in the treatment of this disease over the past 40 years, less than 35% of high-risk patients will survive for 5 years without recurrence [2,3]. Researchers at The Children's Hospital of Philadelphia (CHOP) and Dana Farber developed

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a program of intensive induction chemotherapy followed by tandem myeloablative treatments with peripheral blood stem cell rescue (PBSCR) for treatment of advanced neuroblastoma [4]. With this regimen, researchers are beginning to improve outcomes for this disease. The investigators recently reported that the overall survival rate was 60% at 5 years and 53% at 7 years [5]. With increasing survival rates, it is important to begin to characterize the late effects of treatment in this novel population of survivors.

Currently, there is limited information on late effects in patients with neuroblastoma treated with tandem transplants [6]. This describes the long-term clinical late effects specific to survivors of stage IV neuroblastoma who were all similarly treated using tandem autologous transplantation with PBSCR.

METHODS

Medical records of neuroblastoma patients treated with tandem transplant at CHOP were examined. A total of 35 patients received tandem transplant including total body irradiation (TBI) between 1997 and 2001. Eighteen of the 35 patients died of progressive disease, and 4 are alive with no evidence of disease but are no longer followed at CHOP. All 13 of these patients have been seen in our Multidisciplinary Cancer Survivorship Clinic by a consistent group of subspecialists, including oncology, cardiology, endocrinology, pulmonary, psychology and nutrition [7].

The medical records were reviewed for treatment information and long-term complications. The diagnosis of growth hormone deficiency (GHD) was based upon decelerating growth velocity and biochemical confirmation. Hypothyroidism was diagnosed upon elevation of thyrotropin (TSH). Hypogonadism was diagnosed by failure to enter puberty with elevation of gonadotropins or low gonadotropins and low levels of gonadal steroids. Adrenal insufficiency was based upon failure to increase cortisol with corticotropin releasing hormone (CRH).

A representative subset of electrocardiograms (ECGs) was reviewed including: (1) the first ECG performed at or near the time of diagnosis, (2) the ECG performed closest to 1 year post completion of therapy, (3) the ECG closest to 6 years post completion of therapy, and (4) the most recent ECG. Reports from all echocardiograms, holter monitors, exercise stress tests, and cardiac consultations were also reviewed to identify clinically significant abnormalities.

To assess for pulmonary disease, patients had standard pulmonary function tests (PFTs) done including spirometry and lung volume measurements. Each patient's dentist completed a questionnaire addressing the presence or absence of root stunting, microdontia, and agenesis. In addition, results of Panorex (full mouth X-ray) films were included when available.

Each subject underwent a nutritional assessment by a licensed dietitian. The anthropometric indices that were used to assess growth included Body Mass Index (BMI) for age and weight for age [8]. Identified late effects were classified further by severity/grade using the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0. This was done retrospectively as has been done previously with Versions 2.0 and 3.0 [9,10].

RESULTS

Demographics and Treatment History

All 13 patients (11 males and 2 females) had a diagnosis of Stage IV neuroblastoma. Median age at diagnosis was 22 months (range 13–72). Median time since diagnosis is 9 years (range 7.5–10.5). Median current age of these survivors is 11.5 years (range 9.5–14.5).

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All survivors underwent induction therapy with five cycles of standard agents including cisplatin, carboplatin, cyclophosphamide, etoposide, doxorubicin, and ifosfamide. Resection of the primary tumor and local radiation was followed by two consecutive courses of myeloablative therapy (including total body irradiation) with PBSCR. Cumulative doses are summarized in Table I.

Late Effects

Long-term complications were noted in all 13 patients. All 13 experienced more than one complication, 12 experienced more than 3, and 8 experienced more than 5. The median number of late effects per subject was 6 (range 2–8 late effects). The long-term complications observed are summarized in Table II. Hearing loss and dental abnormalities were the most prevalent complications, followed by growth hormone deficiency and hypothyroidism.

Cardiac

Cardiovascular studies were performed on 12 subjects. All 12 subjects had reports from 2 to 12 echocardiograms for review. Eleven of the 12 subjects had at least one holter to review. Review of these cardiac studies identified one patient with first-degree atrioventricular block. Otherwise, none of the patients demonstrated clinically significant cardiovascular changes such as a prolonged QTc on concurrent ECGs, arrhythmias, ventricular hypertrophy or dilatation, or diminished systolic shortening.

Pulmonary

A total of 12 patients who were followed had one or more sets of PFTs with spirometry and lung volumes. Of this group 7 had normal results while 5 demonstrated mild to moderate restrictive lung disease after therapy. Of the group that developed restrictive lung disease 2 showed evidence of obstructive lung disease as well.

Endocrine

Of the 13 children, 7 were diagnosed with GHD. However, all of the children were short with heights below the mean for age and gender (expressed as standard deviation from the mean for population data). The mean height of the entire cohort at the time of their most recent visit or just prior to growth hormone therapy in the 7 GHD children was −1.89 SD (±0.9) with the tallest having a height of −1.0 SD. The children diagnosed with GHD were shorter in comparison to those who were not diagnosed with GHD (−2.8 SD ±0.73 and −1.68 ±0.53) but due to the small number of patients this finding only approached statistical significance (P =0.07). Before treatment with growth hormone the growth velocity in the GHD patients was slow (−1.2 SD ±1.78) but responded well to standard doses of growth hormone (0.3 mg/kg/week). The first year growth velocity was +2.7 SD (more than 2 SD above the mean for population growth velocity for age and gender).

Other endocrine issues were identified including 7 of 13 with hypothyroidism on thyroid replacement therapy (of whom 5 also had GHD). In those 8 children with an appropriate age for puberty (>10 years for girls, >11 years for boys), 4 entered puberty spontaneously, one has not done so but gonadotropins are normal. There was one patient with precocious puberty and 2 have hypogonadism. One patient demonstrated adrenal insufficiency.

Nutrition

Calculated z scores for all patients not only revealed short stature but also that subjects were underweight for their age. Although patients were proportioned in most cases, and the BMI percentage was essentially normal, the Z scores for BMI and weight for age were all

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significantly abnormal. The range of z scores for BMI and weight for age was −3.17 to 1.47 (−0.4 SD ±1.3) and −3.97 to 0.4 (−1.3 SD ±1.2) respectively.

Dental Outcomes

Completed questionnaires were returned from 12 of 13 dental providers. 11/13 survivors had significant dental sequelae including root stunting, microdontia, and missing teeth. Two of the survivors with no identified late effects to date had not had Panorex films and therefore, root stunting could not be confirmed. The one patient for whom dental records could not be obtained had significant dental changes that were noted by other health care providers in the medical record including missing teeth and microdontia.

Bone Outcomes

Osteochondromas were the most common bony change noted in this population. Six of thirteen (46%) survivors had at least one lesion. Several had numerous osteochondromas. Many of these were found incidentally on chest X-ray or other radiographic studies and others were found because of complaints of pain. Common locations for lesions included the ribs, scapula, and tibia. One patient required surgical excision of an osteochondroma.

Cataracts

Seven of 13 patients have cataracts. None of these patients have required cataract removal to date.

Hearing

Twelve of 13 have sensorineural hearing loss. Of these 12, seven use hearing aids, and all have preferential seating in the classroom.

Nevi

Nine of 13 have an increased number of nevi noted on physical exam. These patients are followed yearly by dermatology for signs of dysplasia. There are no reported secondary skin cancers in this population to date.

Second Tumors

One patient was diagnosed with a pheochromocytoma after presenting with refractory hypertension. The pheochromocytoma was not malignant and was surgically removed.

Renal

All patients had normal serum creatinine values over the last 3–5 years. During this time period, three patients have demonstrated persistent trace hematuria and/or proteinuria. Five of 13 patients have hypertension. None of these patients have received medical intervention.

DISCUSSION

Hearing loss and dental abnormalities were the most prevalent outcomes for the patients in our study, impacting >90% of survivors. Dental changes are not an unexpected outcome secondary to TBI and chemotherapy [11]. Holtta et al. noted that children treated between the ages of 3.1–5 years had the most dramatic dental effects of their cancer therapy [12,13]. Dental changes have been noted after less intense, non-ablative therapies, but not at the severity and frequency of the current transplant population [14,15]. Laverdiere et al. [9] reported on 63 patients treated for advanced stage neuroblastoma, in this group the dental complications were only noted in

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13%, though the treatment of this cohort was more heterogeneous and only 56% of this cohort had an autologous transplant.

An obligatory component of treatment for high-risk neuroblastoma includes cisplatin and carboplatin, known ototoxins. Over 90% of the subjects in this study had documented hearing loss, with significant hearing loss (Grade 3–4) in 58% of the cohort. This finding is similar to or higher than previous literature [6,16–18]. Flandin et al. [6] reported significant hearing loss in only 15% of a cohort of neuroblastoma survivors treated with 360–400 mg/m^2 of cisplatin (±TBI). However, Parsons et al. [17] reported on a cohort of patients, most of whom had received two cycles of high-dose cisplatin in induction therapy followed by a non-TBI transplant regimen using intensified carboplatin (2 g/m^2). Grade 3–4 hearing loss in this cohort was 82%. Several factors may explain the high rate of significant hearing loss in our study population, notably high dose carboplatin. Moreover, schedule of drug administration may play a role. The patients in our current cohort received 200 mg/m^2 per course. Data in the literature suggest that hearing loss may be more significant when cisplatin is administered in this manner rather than two courses of 100 mg/m^2 [19]. Additionally, young age of exposure may also have contributed to the rate of significant hearing loss [20,21]. The use of ototoxic antibiotics for supportive care on therapy must also be considered as a possible contributing factor. Unlike many of the other long-term sequelae identified in our cohort, exposure to TBI is not the primary causative factor for hearing changes, as there is no literature, which associates hearing loss with TBI in the absence of platinum drug exposure. Ototoxicity is a serious problem in this population of survivors. Gurney et al. [22] recently reported that neuroblastoma survivors with significant hearing loss are at elevated risk for learning difficulties and psychosocial problems.

One of the most striking late effects in this cohort is short physical stature, as none of the subjects had attained a height within the average range for their age. Below average height was noted even when subjects were not diagnosed to be GHD. Despite adequate GH replacement in the patients with GHD, they do not grow as well as patients with isolated GHD, since their long bones have been irradiated as part of the treatment regimen [23,24]. Reports on the long-term outcomes of neuroblastoma survivors who were treated with a single autologous transplant including TBI had similar rates of short physical stature [18,25]. The incidence of hypothyroidism the present cohort is consistent with numerous reports in the literature that have reported the negative impact of TBI on thyroid function [6]. In patients treated with a single TBI containing transplant the incidence of hypothyroidism was lower than our cohort, but the median follow up time was significantly shorter [18].

From a nutritional perspective, our results demonstrated that this predominantly male cohort is underweight for age. This is consistent with the report by Meacham et al. [26] which found that male survivors of neuroblastoma in the CCSS cohort were more likely to be underweight as adults compared to sibling controls. These patients warrant anticipatory guidance regarding balanced nutrition and further monitoring regarding health consequences of abnormal BMI.

Musculoskeletal changes are not unexpected in children treated with radiation, including an increased prevalence of osteochondromas [27,28]. Taitz et al. [27] noted the overall risk of osteochondromas to be 24% after TBI, especially when the child was under the age of 5-year at time of treatment. When compared to previous studies, a larger percentage of patients in this study (46%) developed bony changes consistent with osteochondromas [18]. One possible explanation is that the majority of osteochodromas found in our cohort were identified on routine radiographs performed for other tests, rather than when these deformities became painful or interfered with functional mobility.

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Our data do not show any significant cardiac changes in this population. However, given that these survivors are just now within the first decade post treatment, the absence of significant cardiac toxicities should be viewed with cautious optimism. Although the cumulative dose of anthracylines in this treatment regimen is not high, the additive risks of TBI and young age at exposure support the need for longer follow up of cardiac function. In addition, although there is only one second tumor (a pheochromocytoma), the actual incidence of secondary tumors may increase further with time. Secondary hematological malignancies were not seen in this cohort. Similarly, in follow-up of 97 patients treated according to this protocol, one patient has presented with a myelodysplastic picture [5]. One factor that may account for the low risk of secondary hematologic problems seen to date is the decision to collect PBSC early in therapy, where exposure to DNA-damaging agents is less than at the end of induction.

In summary, 13 survivors have significant long-term effects involving multiple systems that have the potential to negatively impact quality-of-life. The importance of continued vigilance with this cohort is evidenced by the fact that these patients already face significant challenges in the first decade after transplant. Moreover, the present results support and extend previous observations that TBI is a major contributor to long-term, multi-organ toxicities [18]. It will be critical to study in a comprehensive manner the newer cohort of advanced stage neuroblastoma survivors who have been managed without TBI. This study is somewhat limited as these data are largely descriptive, and the small number of patients does not allow for high-powered statistical analyses. However, unlike other descriptive studies on outcomes for patients with stage IV neuroblastoma, these patients were uniformly treated, and were followed by the same subspecialists for their late effects of treatment. This highlights the strength of a consistent, collaborative multidisciplinary approach to late effects research, particularly in populations with multiple chronic treatment related toxicities.

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TABLE I

Treatment Summary

	Dose median (range)
Chemotherapy	
Carboplatin	1 g/m^2 (0.7–1)
Etoposide	1.35 g/m^2 (0.95–2.4)
Doxorubicin	150 mg/m^2 (60–150)
Cyclophosphamide	4 g/m^2 (2.9–5)
Ifosfamide	10 g/m^2 (7.2–10)
Cisplatin	200 mg/m^2 (144–400)
Local XRT	
Abdominal (n =8)	1,080 cGy[a]
Pelvic (n =1)	1,080 cGy
Flank (n =1)	1,080 cGy
Adrenal (n =2)	1,080 cGy
Ethmoids and orbits (n =1)	1,080 cGy
Transplant #1	
Etoposide	2.4 g/m^2 (1.7–2.4)
Carboplatin	2 g/m^2 (1.4–2)
Cyclophosphamide	3.6 g/m^2 (2.5–3.6)
Transplant #2	
Melphalan	180 mg/m^2 (126–180)
Total body irradiation	1,200 cGy

[a] One patient received 600 cGy.

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TABLE II

Late Effects

Late effects	No. of patients (%)	Grade 1–2	Grade 3–4
Endocrine			
Primary hypothyroidism	7 (53.8)	7	0
Ovarian failure	2 (15.4)	0	2
Growth hormone deficiency	7 (53.8)	7	0
Sensory			
Hearing Loss	12 (92.3)	5	7
Cataract	7 (53.8)	7	0
Musculoskeletal			
Slipped capital femoral epiphysis	1 (7.7)	0	1
Osteochondroma	6 (46.2)	6	0
Pulmonary			
Restrictive disease	5 (38.5)	5	0
Obstructive disease	2 (15.4)	2	0
Gastrointestinal			
Hepatitis C	0	0	0
Chronic diarrhea	3 (23.1)	3	0
Dental	12 (92.3)	0	12
Renal			
Hypertension	5 (38.5)	5	0
Chronic proteinuria/hematuria	3 (23.1)	3	0
Cardiovascular			
Cardiomyopathy	0	0	0
Conduction abnormalities	1 (7.7)	1	0
Second neoplasms	1 (7.7)	0	1