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Infectious Complications in the First Year Following Autologous Hematopoietic Progenitor Cell Rescue for Children With Brain Tumors

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Background. High-dose chemotherapy with autologous hematopoietic progenitor cell rescue (AuHPCR) for pediatric patients with brain tumors has become an important therapeutic modality to avoid or delay the long-term effects of cranial irradiation. Data on post-AuHPCR infectious complications in this population are lacking. This single institution retrospective review reports the prophylactic practices and infections in the first year following AuHPCR in pediatric patients with brain tumors. ***Procedure.*** The medical record of patients who underwent AuHPCR for the treatment of a malignant brain tumor at Children's Hospital Los Angeles between 1988 and 2010 were reviewed. Patients without prior irradiation who were free of disease at 1 year without additional chemotherapy were evaluated for all infectious disease complications occurring from time of neutrophil engraftment to 1 year post-AuHPCR. ***Results.*** Forty-three of the 115 eligible patients were included. The median time to neutrophil engraftment was 11 days (range: 8–43 days), and 20 Grade III/IV (no Grade V) infectious episodes developed in 15 patients (35%). Fourteen episodes of bacteremia (70%) were catheter-related, predominantly gram-negative (71%), and polymicrobial (50%). There were no fungal or pneumocystis infections and only 1 of 25 (4%) at-risk patients developed VZV reactivation. ***Conclusions.*** These data suggest patients with brain tumors undergoing AuHPCR have few late-occurring non-catheter-related post-transplant infections indicating that prophylaxis practices were sufficient. Central lines should be removed soon after engraftment, but those with central line infections should receive adequate treatment including gram-negative coverage. In addition, only at-risk patients who receive further irradiation may benefit from VZV reaction prophylaxis. Pediatr Blood Cancer 2013;60:2012–2017.

Key words: autologous; catheterization; central venous/adverse effects; hematopoietic transplantation/adverse effects; opportunistic infections/prevention and control; pediatric; peripheral blood stem cell transplantation/adverse effects; transplantation

INTRODUCTION

High-dose chemotherapy with autologous hematopoietic progenitor cell rescue (AuHPCR) for pediatric patients with brain tumors has become more common in the last 20 years in an effort to both improve survival and avoid the long-term effects of cranial irradiation [1–3]. There are limited data regarding immune reconstitution and post-AuHPCR infectious disease rates in pediatric patients treated for brain tumors, with the most recent data reported in 2002 [4]. Current prophylaxis practices in children with malignant brain tumors are primarily based on expert opinion or past experience with infectious disease complications associated predominantly with allogeneic transplantation [5]. Furthermore, published guidelines for infection prophylaxis by the CDC have been met with significant heterogeneity of practice [6].

The aim of this retrospective analysis is to characterize the prophylactic measures utilized and the late (up to 1 year) post-neutrophil engraftment infections in pediatric patients with brain tumors without prior irradiation who underwent AuHPCR at our institution. The prophylaxis methods used at our institution are compared with current CDC guidelines for autologous pediatric patients undergoing transplant, and suggestions are made for supportive care post-AuHPCR in this growing population of patients.

METHODS

Patients

The Center for Clinical Investigation at the Children's Hospital Los Angeles (CHLA) approved this retrospective study. The Autologous Transplant Database at CHLA was interrogated for all children with central nervous system (CNS) malignancies (i.e., medulloblastoma, supratentorial primitive neuroectodermal tumor [sPNET], atypical teratoid/rhabdoid tumor, ependymoma, primary CNS germ cell tumors, choroid plexus carcinoma, and glioblastoma multiforme) treated with marrow-ablative chemotherapy with AuHPCR between 1988 and 2010. Patients who had received prior irradiation, relapsed, died (unrelated to post-transplant infection), died in the pre-engraftment phase, or received additional chemotherapy within 1 year of transplantation were excluded. However, children who received CNS irradiation in the post-engraftment period up to 1 year were included. The medical records were reviewed from the date of hematopoietic cell reinfusion (or the final reinfusion date in patients receiving tandem transplants) until 1 year post-transplantation. The patient characteristics included age, sex, prior therapy, conditioning regimen, progenitor cell source, number of transplantations, and pre-transplant serology of herpes simplex virus (HSV) I and II, VZV, and cytomegalovirus (CMV).

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Definition of Infection

An infectious disease event was defined as a viral, fungal, or bacterial infection that could be confirmed by laboratory testing, radiographic evidence or physical exam and met Common Terminology Criteria for Adverse events version 4.0 grade III or greater criteria. Any incidence of HSV, VZV, or CMV infections or reactivation was also reported. Immune reconstitution tests following AuHPCR are not routinely performed at our institution for this cohort of patients and are subsequently not presented.

Post-Hospital Discharge Supportive Care and Prophylactic Measures

Prior to discharge, patients were instructed in good hand hygiene, relevant antibiotic prophylaxis and to avoid contact with ill individuals; but patients could otherwise return to normal activity depending on physical ability, including attending pre-school, kindergarten, school, or college. *Pneumocystis jiroveci* pneumonia (PJP) prophylaxis included trimethoprim/sulfamethoxazole, dapsone, atavoquone, or pentamidine (aerosolized or intravenous) and started after Day +42. Fungal infection prophylaxis consisted of nystatin or azole antifungals. Prophylaxis of HSV or CMV infections in patients who were seropositive or had a history of suspected exposure to HSV or CMV included acyclovir or gancyclovir. Prophylaxis for VZV reactivation was not routinely prescribed nor was general bacterial prophylaxis. Decisions regarding the removal of catheters were at the discretion of the attending physician but were generally recommended once patients were no longer transfusion-dependent and/or no longer required scheduled intravenous fluids.

Induction and Conditioning Regimens

During the study period, children at CHLA were treated with either the "Head Start" I, II, or III induction chemotherapy regimens followed by a single cycle of marrow-ablative chemotherapy (carboplatin etoposide, and thiotepa) with AuHPCR, or the Children's Oncology Group COG-99703 regimen of three induction cycles of "Head Start I"-like chemotherapy followed by up to three tandem marrow-ablative cycles (thiotepa and carboplatin) each with AuHPCR, or with some combination of these two induction chemotherapy regimens followed by single or tandem cycles of marrow-ablative chemotherapy. The intent in all cases was to avoid irradiation either completely or, in the case of residual tumor, until completion of all marrow-ablative chemotherapy. The details of these chemotherapy protocols have been described elsewhere [7–9].

Statistical Analysis

Descriptive statistics are presented for patient demographics and infectious events and included medians with associated ranges. Data missing from the medical record were omitted from that particular analysis as indicated.

RESULTS

Patients

Between 1988 and 2010, 383 pediatric patients underwent marrow-ablative chemotherapy and AuHPCR at CHLA of whom 115 did so for primary malignant brain tumors. Within the 1-year follow-up period from engraftment, 46 patients relapsed, 6 died of toxicity, and 4 were lost to follow up. A further 12 patients received irradiation before transplantation (either as part of initial therapy or at time of recurrence) and 4 received further maintenance chemotherapy following transplantation. Table I details the characteristics of the remaining 43 patients used in this analysis.

Engraftment and Prophylaxis

The median number of days from transplantation to neutrophil engraftment was 11 days (range: 8–43 days; n = 43). The median length of the post-transplantation course of PJP prophylaxis was 7.7 months (range: 0.8–11.9 months; n = 38) with eight patients (19%) still on prophylaxis at the end of follow-up at 1 year. The median length of the post-transplantation course of fungal prophylaxis was 3 months (range: 0.5–12 months; n = 39) with two patients (5%) still on prophylaxis at the end of follow-up at 1 year. Median viral prophylaxis was 1.8 months (range: 0.5–6 months; n = 20 patients with HSV ± serology).

Infections

Between the time of neutrophil engraftment and 1 year following transplantation 1 Grade IV and 19 Grade III infectious

TABLE I. Patient Characteristics

Characteristics	N = 43
Age at last infusion in years (range)	4.1 (0.8–19.8)
	N (%)
Sex	
Male	23 (53)
Female	20 (47)
Diagnosis	
Medulloblastoma	22 (51)
PNET	7 (16)
Ependymoma	5 (12)
Choroid plexus carcinoma	3 (7)
CNS germ cell tumor	3 (7)
High-grade glioma	1 (2)
Atypical teratoid/rhabdoid tumor	1 (2)
Glioblastoma multiforme	1 (2)
Induction + HD-Cx/AuHPR regimen	
Head Start III	12 (28)
CCG 99703	12 (28)
Head Start II	6 (14)
CCG 9921	3 (7)
Head Start I	3 (7)
ACNS0122	3 (7)
ACNS0333	1 (2)
N/A	3 (7)
Irradiation post-AuHPCR	
None	32 (74)
Craniospinal irradiation (CSI)	6 (14)
Focal only	5 (12)
Type of transplant	
Single	32 (74)
Tandem (x3)	11 (26)
Progenitor cell source	
Peripheral blood	33 (77)
Bone marrow	8 (19)
Peripheral blood + bone marrow	2 (5)

episodes occurred in 15 patients. The 20 infectious episodes included 14 catheter-related bacteremias (4 gram-positive, 10 gram-negative, 50% polymicrobial), and 1 episode each of meningitis, *Clostridium difficile* enterocolitis, VZV reactivation, urinary tract infection (UTI), EBV viremia and tracheitis. Five patients experienced two separate infectious episodes each; and six patients developed polymicrobial infections (range: two to four species). Table II details the infectious episodes that developed for each patient in relation to the AuHPCR conditioning regimen and any subsequent irradiation.

The majority (79%) of post-neutrophil engraftment bacteremias occurred within 90 days of transplantation and were all related to indwelling central venous catheters (CVCs). The median time to development of catheter-related bacteremia was 56 days from transplant (range: 16–180 days) with 57% occurring between 30 and 60 days post-engraftment. The median number of days CVC were in place following transplantation was 97 (range: 0–259 days; $n = 39$).

The single meningitis infection occurred in a patient with a ventriculo-peritoneal shunt (VPS) and represented the only VPS infection among 19 shunted patients. UTI occurred in a patient with spinal cord disease and resulting urinary retention despite receiving bacterial prophylaxis for prior UTIs. The episode of tracheitis was related to prior tracheostomy, and also occurred despite bacterial prophylaxis. The episode of EBV viremia occurred in a 19.8-year-old male 1 day after neutrophil engraftment and resolved within 1 week.

There were 25 patients at risk for VZV reactivation. Of these, 10 were HSV negative and, thus, were not routinely prescribed viral prophylaxis. Seven at-risk patients were irradiated in the post-transplant period, four of whom were prescribed viral prophylaxis and three that were not (due to HSV negativity). The irradiation details of these seven patients are detailed in Table III. The episode of VZV reactivation of the right trigeminal dermatome occurred in an 8.7-year-old patient following 18 Gy craniospinal irradiation (CSI) with a 37.8-Gy involved-field (IF) boost (Table III, Patient 2). The episode occurred greater than 3 months after discontinuation of oral viral prophylaxis, 132 days post-transplantation, and approximately 1 month after completion of radiation therapy. Although he had been transiently pancytopenic during irradiation, he was neither receiving corticosteroids nor was he neutropenic at the time of reactivation. He, like all patients receiving radiotherapy developed significant lymphopenia defined as an absolute lymphocyte count (ALC) less than 500 cells/mm^3 following irradiation. Five of the seven recovered to ALC greater than 1,000 by 6.5 months post-irradiation with two patients still lymphopenic by 1-year post-transplantation (Table III). Both of these patients had received initial induction chemotherapy for mixed germ cell tumors prior to relapse, subsequent re-induction chemotherapy, marrow-ablative therapy and AuHPCR with subsequent irradiation.

DISCUSSION

The use of radiation therapy in the treatment of pediatric CNS tumors has a number of adverse neuropsychological, neuroendocrine, and developmental effects [10]. Therefore, high-dose marrow-ablative chemotherapy protocols with AuHPCR have been implemented to minimize the use of radiation therapy in this population. All patients undergoing marrow-ablative therapy require infectious disease prophylaxis post-transplant; however, patients following AuHPCR are at much lower risk for a variety of post-engraftment infections owing to several factors. It is unknown, however, to what extent prophylaxis practices should differ if at all.

Immune reconstitution has been shown to occur much more rapidly following AuHPCR, as immune markers such as total T-lymphocyte count, Natural Killer cell count, CD8, CD4, and total lymphocyte count may return to normal or peri-normal levels earlier than following allogeneic transplantation [11–13]. The delay in immune reconstitution following allogeneic transplantation is further complicated by immunosuppressive anti-graft versus host disease prophylaxis or treatment. Immune reconstitution also varies based on a patient's age, conditioning regimens, prior infections, graft manipulation, and type of transplantation [14]. In children undergoing AuHPCR, an adequate immune system may reconstitute even faster than immune markers would indicate, as very low rates of opportunistic infection relative to allogeneic transplantation have been reported [4,15–17]. Our cohort obtained neutrophil engraftment in line with other cohorts reported suggesting that immune reconstitution may be similar to those reported [18]. The lack of evidence-based recommendations, however, has led to continued heterogeneity in prophylaxis practices despite published guidelines by the CDC [6]. Our own institutional practices over the study period reflect that heterogeneity very well; however, the lack of serious infectious sequelae have allowed us to discontinue routine immune reconstitution monitoring.

The CDC guidelines detail prophylaxis measures for a variety of opportunistic viral, bacterial, and fungal infections. For pediatric autologous transplants, much of these recommendations are based on extrapolation from adult data. Briefly, the key recommendations for this cohort are repeated here [5]. For patients with HSV seropositivity, acyclovir prophylaxis is given from the first day of conditioning therapy until engraftment occurs or until mucositis resolves whichever is longer (Level of Evidence: BIII). For patients with CMV seropositivity less than 100 days post-transplant gancyclovir is recommended for 3 weeks when antigenemia exceeds five cells per slide (Level of Evidence: BII). For VZV reactivation, acyclovir may be prescribed for 1 year post-transplant, although efficacy data are lacking (Level of Evidence: CII). PJP prophylaxis should be administered for at least 6 months or longer if substantial immunosuppression persists (Level of Evidence: AII). Fungal (*Candida* species) prophylaxis should begin from the day of transplantation until engraftment or until 7 days after the absolute neutrophil count greater than 1,000 cells/mm^3 (Level of Evidence: AI).

In 2002, Benjamin et al. [4] reported infection complications in all pediatric transplants at a single institution which included 102 patients with brain tumors. However, the data reported on patients with brain tumors were not analyzed separately from those patients with other solid tumors. Machatschek et al. [17] reported the post-engraftment infectious disease complications in pediatric patients with solid tumors who underwent marrow-ablative chemotherapy and AuHPCR; however, this report only included three patients with brain tumors. Both of these studies highlighted the presence of CVCs as the greatest risk of post-engraftment infection, although one reported a majority of gram-positive infections while the other reported a preponderance of gram-negative infections.

While catheters are a known risk factor for the development of infection, they have been most frequently associated with gram-positive infections following neutrophil engraftment [17,19]. The incidence of bacteremias in our cohort is similar to that in other

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TABLE II. Post-Engraftment Infections

Patient	Age (years)	Conditioning regimen	XRT	Infectious episodes	Days post-engraftment
1	2.77	Carbo, Thio (3 cycles)	None	(1) *Klebsiella pneumoniae* and *Enterobacter cloacae* bacteremia	7
				(2) *Bacillus* and *Staphylococcus* coagulase negative bacteremia	42
2	1.39	Carbo, Thio (3 cycles)	None	*Klebsiella* and *Enterococcus facelis* and *Enterococcus* Group D bacteremia	82
3	3.98	Carbo, Thio VP-16 (1 cycle)	None	*Pseudomonas putida*, *Acinetobacter lwoffii*, *Staph* coagulase negative, *Agrobacterium* bacteremia	33
4	1.69	Carbo, Thio (1 cycle), Carbo, Thio, VP-16 (1 cycle)	None	*Pseudomonas mendocina* and *Xanthomonas* bacteremia	35
5	3.3	Carbo, Thio, VP-16 (1 cycle)	59.4 Gy IF	(1) *Pseudomonas putida* and *Acinetobacter calcoaceticus* bacteremia	39
				(2) Gram negative rods bacteremia	139
6	2.81	Carbo, Thio, VP-16 (1 cycle)	None	*Escherichia ferguson*, *Mucoid*, *Pseudomonas auerginosa* bacteremia	45
7	2.61	Carbo, Thio, VP-16 (1 cycle)	None	*Klebsiella* bacteremia	26
8	3.64	Carbo, Thio, VP-16 (1 cycle)	None	(1) *Klebsiella* bacteremia	31
				(2) *Serratia marcescens* meningitis	284
9	2.36	Carbo, Thio (3 cycles)	None	(1) *Klebsiella oxytoca* bacteremia	36
				(2) *Moraxella catarrhalis* tracheitis	192
10	0.85	Carbo, Thio, VP-16 (1 cycle)	None	*Staphylococcus epidermis* bacteremia	46
11	2.28	Carbo, Thio (3 cycles)	None	*Streptococcus pneumoniae* bacteremia	114
12	1.9	Carbo, Thio, VP-16 (1 cycle)	None	(1) *Clostridium difficile* enterocolitis	11
				(2) *Klebsiella pneumoniae* urinary tract infection	43
13	8.68	Carbo, Thio, VP-16 (1 cycle)	18 Gy CSI + Boost	*Herpes Zoster* reactivation	121
14	19.8	Thio, VP-16 (1 cycle)	24 Gy CSI	EBV Viremia	1
15	1.08	Carbo, Thio, VP-16 (1 cycle)	None	*Streptococcus pneumoniae* bacteremia	114

Carbo, carboplatin; Thio, thiotepa; Gy, gray; IF, involved-field; CSI, craniospinal irradiation.

TABLE III. Patients at Risk for VZV Reactivation Who Underwent Post-AuHPCR Irradiation

Patient	Age (years)	Diagnosis	XRT dose	# XRT fractions given	Day XRT completed	Last day of viral PPX	ALC XRT start	ALC XRT end	Months until ALC > 1000
1	3.3	Ependymoma	59.4 Gy IF	33	+97	+31	756	444	2.4
2[a]	8.9	PNET	18 Gy CSI + 37.8 Gy IF Boost	41 (10, 10, 21)	+102	+34	1920	240	4.5
3	4.3	Medulloblastoma	23.4 Gy CSI + 30.6 Gy PF Boost	43 (13, 13, 17)	+122	+51	2660	458	3.9
4	7.1	PNET	18 Gy CSI + 41.4 Gy IF Boost	43 (10, 10, 23)	+119	+278	958	187	4
5	8.2	MGCT	23.4 Gy CSI + 30.6 Gy IF Boost + 12.6 Gy Lumbar Spine Boost	48 (13, 13, 15, 7)	+95	N/A	821	110	6.5
6	8.7	MGCT	24 Gy CSI	32 (16, 16)	+73	N/A	2120	219	>9
7	19.8	MGCT	24 Gy CSI	32 (16, 16)	+69	N/A	2037	261	>9

XRT, radiotherapy; PPX, prophylaxis; ALC, absolute lymphocyte count; Gy, gray; IF, involved-field; PNET, primitive neuroectodermal tumor; CSI, craniospinal irradiation; PF, posterior fossa; MGCT, mixed germ cell tumor. [a]Patient with VZV reactivation on Day +132.

reports [19]. Gram-negative organisms, however, caused 71% of the catheter-related bacteremia episodes. The majority of these infections occurred prior to 90 days, despite 49% of patients possessing a central line past 90 days. Based on these data, long-term central venous access could be maintained safely, if absolutely necessary, after an initial high-risk period, possibly due to improved immunological status.

The rate of VZV reactivation reported here is much lower than in previous reports [4,20,21]. The only episode of VZV reactivation occurred in a patient who had recently completed irradiation in the post-transplantation period (Day +132). Focal and extended-field irradiation have both been associated with the development of lymphopenia. Profound lymphopenia has been described in adult patients treated with focal irradiation for a variety of solid tumors [22], in children receiving cranial irradiation [23], and is dependent on the number of fractions delivered [24]. In 1979, Cumberlin et al. [25] described the development of profound lymphopenia that persisted for years in some cases and T-cell dysfunction in the remaining lymphocytes that persisted for at least 2 months post-irradiation. Harisiadis et al. [23] demonstrated that the majority of the lymphopenia was due to the cranial irradiation rather than spinal irradiation. Thus, patients treated with cranial irradiation (or other focal irradiation) would experience a decrease in circulating lymphocytes as they traversed the irradiated field while subsequent spinal irradiation would reduce marrow capacity. While the first instance is enough to cause significant lymphopenia, further reduction was incurred with spinal irradiation. The fact that the vast majority of patients reported previously had likely received radiotherapy as part of their solid tumor treatment may explain the discordance with the incidence of VZV reactivation observed in our cohort that purposely excluded patients who received prior radiotherapy. Indeed, our observed rate of 14% (one of seven) of patients with prior irradiation and VZV seropositivity who developed VZV reactivation more closely aligns with what has been previously reported, suggesting that the risk of VZV reactivation may be more closely associated with irradiation rather than AuHPCR and that patients who avoid irradiation may not need VZV viral prophylaxis. Instead, those individuals who receive irradiation (focal or extended-field) may benefit from viral prophylaxis to prevent VZV reactivation for 3–6 months post-irradiation based on our data, though our numbers are too small to make a definitive recommendation.

Variation in prophylactic practices was found within our own institution. Of the 39 patients for whom PJP practices were known, 14 received PJP prophylaxis for less than or equal to the time recommended by the CDC. Whereas patients who were placed on fungal or viral prophylaxis were kept on prophylaxis for times longer than recommended. It should be noted that the five patients who received post-transplant supportive care at institutions other than CHLA generally received some of the longest prophylaxis courses within this cohort, with all five receiving PJP prophylaxis for a year or more. Neither PJP nor fungal infections were noted in the entire study population; only one episode of VZV reactivation developed, and the incidence of bacterial infections was no different than similarly reported cohorts [4,17,19–21].

Given the very low rate of non-catheter-related infections, we can conclude that the practices used were adequate, but likely shorter courses of viral and fungal prophylaxis could be used while achieving comparable rates of infection. We admit that the lack of immune reconstitution analyses is a limitation of this study; but

current fungal and viral prophylaxis practices at our institution were adequate to prevent any serious fungal or viral infection in our cohort. Since the majority of serious infectious episodes were catheter-related bacteremias, removal of such catheters should be strongly considered as soon as the patient is no longer transfusion- or intravenous fluid-dependent; however, we found no incidence of *pseudomonal* infections resistant to third-generation cephalosporins. Individuals who are predisposed to infections, such as those with dysfunctional bladders or tracheostomies, may require additional bacterial prophylaxis for longer periods than is currently recommended. Individuals who receive irradiation post-transplantation may benefit from viral prophylaxis to prevent zoster reactivation.

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