Radiotherapy and Oncology 90 (2009) 242–246

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Total body irradiation

Renal toxicity in children undergoing total body irradiation for bone marrow transplant

Natia Esiashvili [a,*], Kuang-Yueh Chiang [b], Michael D. Hasselle [c], Cynthia Bryant [d], Robert H. Riffenburgh [e], Arnold C. Paulino [f]

[a] Department of Radiation Oncology, Emory University School of Medicine, Atlanta, CA, USA
[b] Children's Healthcare of Atlanta, Atlanta, CA, USA
[c] Department of Radiation Oncology, University of Chicago, Chicago, IL, USA
[d] Keyserling Cancer Center, Port Royal, SC, USA
[e] Naval Medical Center, San Diego, CA, USA
[f] Department of Radiation Oncology, Baylor College of Medicine, Houston, TX, USA

ARTICLE INFO

Article history:
Received 13 March 2008
Received in revised form 10 September 2008
Accepted 23 September 2008
Available online 28 October 2008

Keywords:
Total body irradiation
Renal toxicity

ABSTRACT

Purpose: Contribution of total body irradiation (TBI) to renal toxicity in children undergoing the bone marrow transplant (BMT) remains controversial. We report our institutional retrospective study that evaluates the frequency of acute and chronic renal dysfunction in children after using total body irradiation (TBI) conditioning regimens.

Materials and methods: Between 1995 and 2003, 60 children with hematological malignancies underwent TBI as part of a conditioning regimen before allogeneic BMT. Patients received 4–14 Gy at 1.75–2 Gy/fraction in six-eight fractions. Lung shielding was used in all patients to limit lung dose to less than 10 Gy; renal shielding was not utilized. All patients had baseline renal function assessment and renal dysfunction post-BM was mainly evaluated on the basis of persistent serum creatinine elevation at acute (0–90 days) and chronic (>90 days) intervals after completion of BMT.

Results: Acute renal dysfunction (ARD) was documented in 27 patients (45%); the majority had concurrent diagnosis of veno-occlusive disease (VOD) or graft-versus-host disease (GVHD) and other potential causes (sepsis, antibiotic). The risk for delayed renal dysfunction (DRD) at 1 year approached 25% for surviving patients. The ARD was strongly linked with the risk of the DRD. There was no statistically significant relationship between ARD, DRD and underlying diagnosis, GVHD, VOD or TBI doses with both univariate and multivariate analyses. The younger age (<5 years) had significantly increased risk for the development of ARD ($p = 0.011$).

Conclusion: Our analysis validates high incidence of renal dysfunction in the pediatric BMT population. In contrast to other reports we did not find total body irradiation dose to be a risk factor for renal dysfunction. Future prospective studies are needed to assess risk factors and interventions for this serious toxicity in children following allogeneic BM.

Bone marrow transplantation (BMT) is an effective treatment for a wide range of childhood malignancies. Complications are a significant concern, particularly in children with a higher chance of long-term survival. In the first 3 months post BMT, transplant-related mortality in children reaches 10–20% [1–3]. Nephrotoxicity has been reported by a number of institutions as a potential acute and/or chronic complication of BMT; its frequency approaches 20–25% [4–10]. Acute renal dysfunction (ARD) contributing to transplant-related mortality may also develop from such major complications such as opportunistic infections, veno-occlusive disease (VOD), graft versus host disease (GVHD), and recurrence of the primary disease. Some of these patients will ultimately develop chronic renal dysfunction [11–16]. Renal toxicity can manifest as decreased glomerular filtration rate (GFR) with occasional proteinuria and microscopic hematuria, and clinical signs of hypertension and edema.

Studies on renal toxicity in BMT patients have demonstrated an association between TBI and nephrotoxicity, however, most published reports combine data from both adults and children [6,8,17,18]. From reviewing the literature it is hard to determine if age plays a role in susceptibility to renal toxicity, but as with many other critical organs, cancer therapy-related toxicity can vary substantially between adults and children. Determining the prevalence of renal toxicity in children undergoing TBI in modern

* Corresponding author. Address: Department of Radiation Oncology, Emory University School of Medicine, 1365 Clifton Road, NE, Atlanta, GA 30322, USA.
E-mail address: natia@radonc.emory.org (N. Esiashvili).

0167-8140/$34.00 © 2008 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.radonc.2008.09.017

clinical practice is thus very important. Moreover, understanding contributing factors and mechanisms for this serious toxicity may contribute to improved outcome for this high-risk population. Because of the scarcity of reports on renal toxicity in pediatric transplant patients, this institutional study was undertaken to add to the existing data on overall incidence of acute and late renal toxicity for children with high-risk hematological malignancies undergoing allogeneic BMT with a TBI-based conditioning regimen. This report also analyzes the role of risk factors (patient age, underlying disease, type of transplant, GVHD, VOD, TBI dose) in the development of renal dysfunction.

Materials and methods

Between 1994 and 2003, 60 pediatric patients received TBI as part of the conditioning regimen for BMT at the Radiation Oncology Department of Emory University in Atlanta, GA. The predominant disease types were acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). The most common preparative regimens were TBI and cyclophosphamide (Cytoxan) with antithymocyte globulin (ATG) or TBI and cyclophosphamide/cytarabine (Ara-C)/ATG. The patients had no evidence of renal dysfunction prior to transplantation as documented from baseline creatinine levels and Glomerular Filtration Rate (GFR) test results except for one patient who had renal failure prior to BMT and renal transplant was planned as part of the treatment.

Patient characteristics and diagnoses are noted in the Table 1. The median age at the time of diagnosis was 8.4 years (range 0.3–19.6 yr). Follow-up times ranged from 1 to 131 months (median 4.5 mo). The majority of patients in our series were young ($33 < 10$, $19 \leqslant 5$ yr).

TBI doses received ranged from 4 to 14 Gy (median 14 Gy). Forty nine patients received a TBI dose of >12 Gy. In all cases, TBI was delivered twice a day with a minimum 6-h interval between treatments. Patients were treated with linear accelerators in the lateral decubitus position with isocentric anterior-posterior and posterior-anterior fields delivered via extended distance technique. A Plexiglas sheet was placed in front of the patient's couch to reduce the dose build-up in the body. Treatment planning was performed for the calculation of doses to the central axis (at the level of the umbilicus) as well as off-axis points (head, neck, mediastinum, bilateral chest, thigh, and leg). Attenuators were applied to the head, neck, leg, and ankle regions to achieve doses to within 10% of prescribed dose. All patients underwent Computer Tomography (CT) planning to design customized lung blocks to limit the lung dose to 10 Gy. The kidneys and the liver were never shielded.

Table 1
Patient characteristics and diagnosis for 60 children who underwent TBI before allogeneic bone marrow transplant.

	n	(%)
Age (yr)		
Median	8.4	–
Range	0.3–19.6	–
Diagnosis		
ALL	25	42
AML	23	38
CML	5	8
Other hematologic disorder	7	12
Donor type		
Matched sibling	10	17
Mismatched related	16	26
Matched unrelated	34	57
TBI doses (GY)		
<12	11	18
1–14	49	8
Total	60	100

Post-transplant GVHD prophylaxis was given to every patient as cyclosporine or cyclosporine combined with methotrexate. The majority of patients were exposed to potentially nephrotoxic drugs during their post-transplant period, namely cyclosporine, aminoglycosides, vancomycin, amphotericin, and antiviral drugs. Follow-up data on patients were obtained from medical records, with Institutional review board (IRB) approval.

All patients had a complete medical evaluation prior to the BMT including history and physical examination. Laboratory evaluation included complete blood count (CBC) with a differential, blood smear, blood urea nitrogen (BUN), serum creatinine, liver function tests, urinalysis, and chest radiograph. Renal dysfunction was mainly assessed on the basis of serum creatinine elevation after BMT also based on the blood pressure elevation, proteinuria, results of creatinine clearance, GFR and renal biopsies if they were available. Acute renal dysfunction (ARD) was defined as persistent creatinine elevation above the upper limit of normal (>1.2 mg per dl) with or without other positive pertinent tests. Delayed renal dysfunction (DRF) was defined as creatinine elevation (with the same criteria) after 90 days from transplantation.

Statistical analysis

Fisher's exact test was used to calculate the correlation of acute and chronic renal dysfunction with the following individual variables: age, primary diagnosis, development of GVHD and/or VOD, and TBI dose. Since all patients were exposed to nephrotoxic drugs, it was not selected as one of the variables. Patients were censored at relapse (if any) or at last follow-up evaluation. A Kaplan-Meier analysis was performed to calculate the cumulative risk probability of renal dysfunction-free survival (RDFS) at any time. Ninety-five percent confidence intervals (CIs) were also determined.

Results

Thirty-seven patients (62%) died within 1 year after BMT; predominant causes of death were graft failure and infection. Acute renal dysfunction (ARD) developed in 27 patients (45%); 3 patients required dialysis with eventual restoration of renal function. The majority of patients had a concurrent diagnosis of GVHD ($n = 14$) and VOD ($n = 18$). Four of 27 children who died within 3 months after BMT had experienced ARD. All four of these patients had associated hypovolemia, sepsis, or other complications; renal dysfunction was not a proximate cause of their death. Fourteen of 27 patients with ARD survived for more than 100 days post-BMT six of those (43%) eventually developed a DRD. The incidence of ARD was not statistically influenced by underlying diagnosis, donor type, GVHD, VOD, or TBI dose (Tables 2 and 3). On multivariate analysis only age <5 yr was associated with increased risk for ARD.

Of 36 patients (from entire group) who survived for more than 100 days post-BMT, DRD was diagnosed in 9 (25%). As stated above, six of them had the ARD preceding this diagnosis. Clinical characteristics of patients who developed DRD are outlined in Table 4. Two of the nine patients with DRD required major interventions such as hemodialysis or kidney transplant. Of note, one of these two patients was the patient diagnosed with renal failure prior to BMT and it persisted until he underwent planned kidney transplant. None of the DRD patients had radiation nephropathy documented in biopsy or resection specimens. For one patient, renal dysfunction was attributed to Hemolytic-Uremic Syndrome (HUS) and in another one to cyclosporine nephropathy. The ARD was strongest predictor in developing DRD (6 of 9 patients). Neither univariate nor multivariate