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The Impact of Palifermin Use on Hematopoietic Cell Transplant Outcomes in Children

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Clinical trials evaluating palifermin have enrolled few pediatric patients, precluding safety analyses in large groups of children. We compared hematopoietic cell transplantation (HCT) outcomes among pediatric patients who did or did not receive palifermin as a preventive treatment for oral mucositis. Pediatric patients and controls, matched for HCT and donor type, disease, disease status, and age, were selected from the Center for International Blood and Marrow Transplant Research database and a 1:3 matched cohort analysis was performed. Stratified Cox proportional hazards models were built and propensity score adjustments were used to compare overall and disease-free survival outcomes between palifermin-treated and untreated patients. Three controls were identified for 90% of palifermin recipients. The remaining cases were matched with 2 (8%) controls or 1 (2%) control, for a total of 210 palifermin-treated patients matched with 606 controls. Median follow-up was 31 months in cases and 36 months in controls. Fifty-seven percent of patients underwent allogeneic HCT, mostly for acute leukemia, and 43% underwent autologous HCT, mostly for solid tumors. In univariate analyses, 2-year survival and disease-free survival rates after allogeneic HCT (58% versus 66%, $P = .109$; 49% versus 60%, $P = .06$) and after autologous HCT (73% versus 77%, $P = .474$; 60% versus 64%, $P = .637$) were similar between palifermin-treated patients and matched controls. In multivariate analysis, palifermin treatment did not significantly increase the risk of mortality (relative risk [RR], 1.20; 95% confidence interval [CI], .87 to 1.66) or of relapse (RR, 1.12; 95% CI, .78 to 1.62) compared with matched controls. No significant differences in rates of acute or chronic graft-versus-host disease (GVHD) were observed between palifermin-treated patients and matched controls. Among pediatric patients undergoing HCT, overall survival, disease-free survival, neutrophil recovery, and GVHD rates were similar between palifermin-treated patients and matched controls.

INTRODUCTION

Palifermin (a recombinant human keratinocyte growth factor [KGF], Kepivance, Swedish Orphan Biovitrum AB, Stockholm, Sweden) decreases the duration and severity of oral mucositis (OM) after intensive chemotherapy and radiotherapy for hematologic cancers [1,2]. In studies of adults, palifermin also improved daily functioning activities, such as swallowing, drinking, eating, talking, and sleeping, and decreased the use of opioids when compared with placebo [3]. Additionally, when compared with standard of care, palifermin decreased the length of hospitalization, number of nutrition impact symptoms experienced, total parenteral nutrition, and narcotic opioid use, but it appeared to have little impact on infection rates or time to engraftment [4-7]. Palifermin treatment does not appear to affect the incidence and severity of acute graft-versus-host disease (GVHD) [5,8], although 1 small study reported that acute GVHD was less prevalent in patients who received palifermin compared with those who did not [4].

Palifermin, which is an N-truncated human KGF, acts physiologically on cells that express the KGF receptor, stimulating their proliferation, differentiation, and survival [1].

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However, cells of the hematopoietic lineage do not express the KGF receptor, and the administration of palifermin for the prevention of OM in patients with hematologic malignancies does not appear to adversely affect other hematopoietic cell transplantation (HCT) outcomes [9]. However, most of these outcomes, including outcomes pertinent to safety (eg, mortality and count recovery) were largely evaluated in adult patients [2-5]. There are few clinical data on the long-term effects of palifermin in children [10-12]. In 1 study involving children undergoing autologous HCT, palifermin was shown to be effective at preventing OM and contributed to a significant decrease in hospital stays and lower incidence of infections [10]. However, longer-term effects were not studied. To address this knowledge gap, we studied outcomes of children reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) database and compared key safety outcomes between those who were treated with palifermin and those who were not.

PATIENTS AND METHODS

Data Source and Participants

The CIBMTR is a research collaboration between the National Marrow Donor Program/Be The Match and the Medical College of Wisconsin. It comprises a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on allogeneic and autologous HCT. Participating centers are required to report all transplantations consecutively; compliance is monitored by on-site audits and patients are followed longitudinally. Computerized checks for discrepancies, physicians' review of submitted data, and on-site audits of participating centers ensure data quality. Studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. All patients or their legal guardians signed informed consent.

The CIBMTR collects data at 2 levels: transplantation essential data (TED) level and comprehensive report form (CRF) level. The TED-level data is an internationally accepted standard data set that contains a limited number of key variables for all consecutive transplant recipients. TED-level data, with some additional details of donor and graft characteristics, encompasses the data submitted to the Stem Cell Therapeutic Outcomes Database, which is maintained by CIBMTR, and required by federal statute for all allogeneic transplantations in the United States. When a transplantation is registered with the CIBMTR, a subset of patients is selected for the CRF level of data collection through a weighted randomization scheme. The CRF-level captures additional patient-, disease-, and treatment-related data. TED and CRF level data are collected before transplantation, 100 days and 6 months after transplantation, annually until year 6 after transplantation, and biannually thereafter until death.

Eligible patients for this study were 18 years old or younger at time of transplantation for a hematologic malignancy or solid tumor, received myeloablative allogeneic or autologous HCT in a center in the United States, and had their outcomes were reported at the CRF level to the CIBMTR from 2005 and 2012. We attempted to match all pediatric patients treated with palifermin who met the inclusion criteria to a control patient in a 1:3 palifermin to control ratio. Matching variables included transplantation type (autologous versus allogeneic), donor type, and disease type and status. Patients matched for these variables were considered a possible matched control if (1) both patients' ages were $<$ 2 years old with an age difference $\leq$ 1 year, or if (2) both patients' ages were $>$ 2 years old with an age difference of $\leq$ 5 years. Matched controls were selected with the smallest age differences among all potential matched controls.

The prematching study cohort consisted of 216 patients who were given palifermin and 4287 patients with no palifermin exposure. Matching at 1:3 was successful for 90% of pairs (n = 190 pairs); the remaining pairs were matched at 1:2 (8%; n = 16 pairs) or 1:1 (2%; n = 4 pairs), for a total of 816 patients and 210 matched pairs. Six palifermin cases could not be matched to any controls.

Endpoints

Overall survival was estimated as the interval from HCT to death from any cause. Disease-free survival was calculated as the interval from HCT to time of disease relapse or death from any cause. *Relapse* was defined as the onset of recurrent disease after a documented complete remission. Risk of relapse was estimated using cumulative incidence function, with death in remission treated as the competing risk. *Transplantation-related mortality* was defined as time to death from any cause while in remission, and disease relapse was considered a competing risk. Acute GVHD was diagnosed and graded based on consensus criteria, and chronic GVHD was diagnosed based on clinical criteria [13,14]. *Neutrophil recovery* was defined as time to an absolute neutrophil count $>$ .5 $\times$ 10^9/L (first of 3 consecutive days). Neutrophil recovery and GVHD events were estimated using cumulative incidence function, treating death without the event as a competing risk. Data on efficacy outcomes of palifermin (such as the incidence of OM after HCT, narcotic use, quality-of-life during the transplantation process and enteral/parenteral nutrition use), are not collected on CIBMTR data collection forms and, hence, not analyzed in the current study, which focused on safety.

Analytic Methods

Stratified Cox proportional hazards models were constructed on matched pairs. Propensity scores were used to further adjust for covariates in the multivariate analysis. Covariates analyzed to derive the propensity scores were age, sex, race, Karnofsky/Lansky performance score (KPS/LPS), disease/disease status, conditioning regimen, donor type, donor-recipient cytomegalovirus match, donor-recipient gender match, antithymocyte globulin use, GVHD prophylaxis, year of HCT, and transplantation type. The final propensity score model included KPS/LPS, antithymocyte globulin use, conditioning regimen, cytomegalovirus match, and donor type. The propensity score is the probability of a particular patient receiving palifermin treatment given the patient's individual characteristics [13-16]. If accurately modeled, one can adjust for many observed confounders and obtain a less-biased estimate of the effect of an exposure on an outcome by including the propensity scores in a multivariate regression model. In this study, the logistic regression model used for the propensity score was $\text{logit}(\pi_i) = \alpha + \boldsymbol{\beta}\mathbf{Z_i}$, where $\pi_i = P(Y_i = 1)$ for $Y_i = 1$ if the ith patient received palifermin or $Y_i = 0$ if they did not, and $\mathbf{Z_i}$ represented the covariates listed. Using this model, the predicted propensity score was calculated for each patient based on his/her characteristics. Equal propensity scores indicated patients with similar probabilities of being treated with palifermin. The distributions of estimated propensity scores (Table 1) were significantly different between palifermin-treated and control patients ($P < .0001$) overall and including autologous ($P = .0268$) and allogeneic HCT recipients ($P < .0001$) separately. Within the model, adjustment with the propensity score was used while estimating the impact of palifermin use for each clinical outcome.

RESULTS

Patient Disposition and Demographics

Most patients were Caucasian (77%), male (60%), and had a KPS/LPS $\geq$ 90 (73%) (Table 2). The median ages at transplantation were 9 years for all patients, 11 years for allogeneic HCT recipients, and 5 years for autologous HCT recipients.

The median follow-up times of survivors were 31 months for patients treated with palifermin and 36 months for controls. Forty-three percent of patients underwent autologous HCT, mostly for solid tumors. Patients who underwent autologous HCT were mostly treated with BCNU, etoposide, cytosine arabinoside, and melphalan (BEAM) or similar BEAM-like or thiotepa-based regimens. Forty patients treated with palifermin received BEAM/BEAM-like conditioning followed by autologous HCT for neuroblastoma (NB) (n = 30), Hodgkin disease (HD) (n = 8), and other solid tumors (n = 2). Twenty five patients received thiotepa-based regimens for NB

Table 1
Propensity Scores for Palifermin-Treated Patients and Controls Who Underwent Autologous or Allogeneic HCT

HCT	Palifermin		Control		*P* Value
	n	Median (range)	n	Median (range)	
Autologous	90	.25 (.16-.33)	257	.25 (.16-.33)	.0268
Allogeneic	120	.34 (.01-.87)	349	.17 (.01-.74)	$<$ .0001
All	210	.26 (.01-.87)	606	.25 (.01-.74)	$<$ .0001

Propensity scores (PS) for autologous (% of palifermin versus control): PS = .16 (7% versus 13%); PS = .25 (61% versus 65%); PS = .33 (32% versus 22%).