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Long-Term Safety Outcomes in Patients with Hematological Malignancies Undergoing Autologous Hematopoietic Stem Cell Transplantation Treated with Palifermin to Prevent Oral Mucositis

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A B S T R A C T

The purpose of our study was to compare long-term safety outcomes (overall survival, disease progression, and incidence of secondary malignancies) between palifermin and placebo in the prevention of oral mucositis in patients with hematological malignancies undergoing autologous hematopoietic stem cell transplantation (HSCT). Patients were enrolled between 1997 and 2005 into 4 phase I to III studies (3 double-blind placebo-controlled and 1 open-label) conducted at 31 sites in Australia, Europe, and the United States. Survival outcomes (overall survival, progression-free survival) were compared using hazard ratios (HRs) estimated with a Cox model that included treatment group, baseline age, disease type, Eastern Cooperative Oncology Group performance status, country, and presence of prior radiotherapy as covariates. The incidence of secondary malignancies was compared with a chi-square test. A total of 672 patients were randomized into the studies (428 palifermin and 244 placebo). The median follow-up time for subjects alive at last visit was 7.9 years (range, .1 to 14.9) for palifermin and 8.8 years (range, .1 to 14.8) for placebo. Palifermin-treated patients had overall survival (HR, 1.01; 95% confidence interval [CI], .78 to 1.31; $P = .921$) and progression-free survival times (HR, 1.04; 95% CI, .83 to 1.31; $P = .733$) that were comparable with placebo-treated patients. Secondary malignancies were reported by 13% of palifermin-treated patients versus 11% of placebo patients ($P = .477$). Breakdown into secondary hematological malignancies (7% versus 6%) or solid tumors (6% versus 6%) did not suggest any differences between the treatment groups. After a follow-up of up to 15 years, comparable long-term safety outcomes (overall survival, progression-free survival, and incidence of secondary malignancies) were observed for palifermin- and placebo-treated patients undergoing autologous HSCT.

INTRODUCTION

Treatments for malignancies with chemotherapeutic agents and/or radiotherapy are becoming increasingly effective but are associated with short- and long-term side effects, including complications such as oral mucositis (OM) [1]. OM typically appears 7 to 14 days after the start of chemotherapy or with radiotherapy at a cumulative tissue dose of 15 Gy to 20 Gy of standard fractionated radiation therapy [2]. The incidence of ulcerative OM ranges between 20% and 80%, depending on the cancer treatment [3,4], but patients undergoing chemoradiotherapy for hematological malignancies have an incidence closer to 100% [5]. Clinical features of OM include erythema, ulceration, and pseudomembrane formation, which can lead to pain, difficulty in swallowing and chewing food, and increased risk of

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infections [6]. Severe symptomatic OM can also contribute to therapy interruption and increased antibiotics and narcotics use, hospitalization time, and overall treatment cost [6].

Over the years, various drugs and methods have been investigated to treat and prevent OM. For patients undergoing hematopoietic stem cell transplantation (HSCT) for treatment of chemosensitive malignancies, such as multiple myeloma and non-Hodgkin and Hodgkin lymphomas, successful therapies include oral cryotherapy [7], low-level light laser therapy [8], and palifermin [1,9]. Palifermin (Kepivance, Swedish Orphan Biovitrum AB [Sobi], Stockholm, Sweden) has been shown to reduce the incidence and duration of severe OM in patients undergoing HSCT, improve swallowing problems and nutrition, and decrease length of hospital stay and narcotic opioid use compared with placebo [10-14]. However, palifermin had no impact on rates of infection, dietary intake, or time to engraftment [12]. Overall, palifermin has been shown to be well tolerated and safe for patients in shorter follow-up studies [5,10,15,16].

Palifermin, which is an N-truncated human keratinocyte growth factor (KGF) produced by recombinant DNA technology, has improved protein stability over endogenous human KGF [17]. It acts physiologically on cells that express the KGF receptor, stimulating their proliferation, differentiation, and survival [17]. Unlike cells of mesenchymal origin, cells of the haematopoetic lineage do not express the KGF receptor, and the administration of pharmacologic doses of palifermin for the prevention or treatment of OM in patients with hematologic malignancies is not suspected to have adverse effects on the promotion of secondary haematological malignancies. However, the incidence of secondary malignancies and mortality because of malignancies of epithelial cell origin could potentially be higher in patients treated with palifermin.

Regardless, patients undergoing high-dose chemo/radiotherapy and autologous HSCT are at significant risk for developing a secondary malignancy [18], and because palifermin is intended as a supportive care agent, it is important to evaluate its effects on long-term safety outcomes. The objective of this study was to compare long-term safety outcomes (overall survival, progression-free survival, and incidence of secondary malignancies) of palifermin versus placebo when used to prevent OM in patients with hematological malignancies undergoing autologous HSCT.

PATIENTS AND METHODS

Study Design and Participants

Patients with hematological malignancies undergoing high-dose chemotherapy with or without total body irradiation followed by autologous HSCT were initially enrolled in 4 phase I to phase III studies (3 double-blind placebo-controlled studies [5,15,16] and 1 open-label study (unpublished data)) conducted at 31 sites in Australia, Europe, and the United States between 1997 and 2005 (Table 1). Patients were eligible for participation in a long-term follow-up study if they had received at least 1 dose of investigational product regardless of treatment group assignment in any of the 4 parent studies. All subjects were required to give written informed consent to be enrolled in the parent study as well as in the follow-up study. Patients were followed from the beginning of the above mentioned clinical studies to the time of the study closure (2012).

Analytic Methods

Demographic data, subject baseline characteristics, and exposure to investigational product were collected in the parent studies. Demographic and baseline characteristics were compared between treatment groups using either a *t*-test (continuous variables), a chi-square test (categorical variables), or Fisher's exact test (categorical variables with small cell size).

Survival status (dead or alive, disease progression or no progression) of all treated patients were included to their last follow-up time, whether in the parent study or in the follow-up study. Data on secondary malignancies were available only for the patients enrolled in the follow-up study and up until their last follow-up time.

Survival outcomes (overall survival and progression-free survival), beginning from the date of first palifermin infusion, were compared using hazard ratios (HRs) estimated using a Cox model that included treatment group, baseline age, disease type (Hodgkin lymphoma, non-Hodgkin lymphoma, multiple myeloma, leukemia), Eastern Cooperative Oncology Group performance status, country, and presence of prior radiotherapy as covariates. Because the covariates included in the Cox models were not predefined, stepwise multivariate Cox models were used as an initial step to select the covariates to be used in the final Cox models. All demographic and baseline characteristics collected in the studies were included in this process as potential explanatory factors. Forward selection steps followed by backward elimination steps were used on a 2-sided significance level of .10 for both selection and elimination. For time to cancer-related death, deaths preceded by disease progression or development of a secondary malignancy were classified as events, whereas deaths from other reasons were censored. For time to non–cancer-related deaths, death preceded by disease progression or development of a secondary malignancy were censored, whereas death due to other reasons were classified as events.

In addition to the HR estimates calculated with the adjusted Cox model, the survival outcomes were described with unadjusted Kaplan-Meier plots. Incidence of secondary malignancies was compared using a chi-square test.

RESULTS

A total of 672 patients were randomized to the parent studies, with 662 patients receiving at least 1 dose of palifermin or placebo (Figure 1). A total of 543 patients participated in the long-term follow-up study and were followed for secondary malignancies. However, data from all 662 patients were used for the analysis of overall survival and progression-free survival times.

Overall median follow-up time among the patients who were alive at the last contact was 8.2 years (range, .1 to 14.9) for a total of 3557 cumulative follow-up years. Median follow-up time was 7.9 years (range, .1 to 14.9) for patients in the palifermin group and 8.8 years (range, .1 to 14.8) for patients in the placebo group (Table 2). The mean age of patients was 45 years (Table 3), and the majority were male (63%), Caucasian (84%), diagnosed with non-Hodgkin lymphoma (71%), and had an Eastern Cooperative Oncology Group performance status of 0 (70%). Compared with the placebo group, more patients in the palifermin group were diagnosed with non-Hodgkin lymphoma (73.9% versus

Table 1
Study Descriptions

Study	Phase	Randomization (Palifermin:Placebo)	Design	Study Endpoints
1 [15]	I/II	2:1	Double-blind, multicenter, dose-escalation	Safety and tolerability of palifermin
2 [16]	II	2:1	Double-blind, multicenter	Efficacy and safety of palifermin
3 [5]	III	1:1	Double-blind, multicenter	Efficacy and safety of palifermin
4	I	N/A	Open-label, single-center	PK profile of palifermin

PK indicates pharmacokinetic.