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Phase I Trial of Parathyroid Hormone to Facilitate Stem Cell Mobilization

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ABSTRACT

Autologous stem cell transplantation is a curative procedure for many patients with lymphomas, and has been shown to improve survival in patients with multiple myeloma. Approximately 20% of patients are unable to mobilize sufficient hematopoietic stem cells to proceed safely to autologous stem cell transplantation. Parathyroid hormone (PTH) affects osteoblasts and the stem cell niche, and has been shown to improve survival when given posttransplant in a mouse competitive transplant model. In this Phase I study, 20 subjects who had 1 or 2 unsuccessful stem cell mobilization attempts, received PTH in escalating doses of 40 μg, 60 μg, 80 μg, and 100 μg for 14 days. On days 10-14 of treatment, subjects received filgrastim 10 μg/kg. The PTH was tolerated well and there was no dose-limiting toxicity. Forty-seven percent of subjects who had failed 1 prior mobilization attempt met the mobilization criteria of >5 CD 34$^+$ cells/μL in the peripheral blood. Forty percent of subjects who failed to reach adequate CD34$^+$ cell counts in 2 prior mobilization attempts met the mobilization criteria. PTH was well tolerated at doses up to 100 μg in human cancer patients. The efficacy of PTH for mobilization of hematopoietic stem cells will need to be tested in a larger Phase II study.

KEY WORDS

Parathyroid hormone • Mobilization • Stem cells

INTRODUCTION

Chemotherapy followed by growth factor administration has become a standard strategy for mobilization of peripheral blood stem cells (PBSCs) in preparation for autologous stem cell transplantation [1,2]. Regardless of the mobilization strategy, approximately 10%-20% of patients fail to collect an adequate number of stem cells to ensure engraftment [3,4]. Predictive factors for poor mobilization have been studied and include age >70 years, >12 months of prior therapy, and platelet count $<200 \times 10^9$/L prior to mobilization [4]. Poor mobilization of PBSCs has also been associated with worse transplant outcomes in lymphoma patients [5].

Studies in mouse models have been undertaken to try to understand the stem cell niche, and thereby increase stem cell numbers. Osteoblasts are a regulatory component of the hematopoietic stem cell niche and can be targeted as a means to increase stem cell numbers [6,7]. Osteoblasts produce hematopoietic growth factors and are activated by parathyroid hormone (PTH) or the locally produced, PTH-related protein (PTH-rP), through the PTH/PTHrP receptor (PPR) [8,9]. The Notch signaling pathway regulates cell fate in a wide variety of systems including hematopoietic self-renewal [10]. Furthermore, the Notch ligand Jagged 1 is expressed by marrow stromal cells and murine osteoblasts, and is increased with PPR activation [6]. It is one of several potential molecular mechanisms by which osteoblast stimulation may alter stem cell numbers [11,12].

Using either a genetic model where the PPR was constitutively active in osteoblasts or a pharmacologic

model where PTH(1-34) was used to activate PPR, the Scadden laboratory has demonstrated a 2-fold increase in hematopoietic stem cells in murine bone marrow. This resulted in increased ability to engraft irradiated recipient animals when either bone marrow or granulocyte colony-stimulating factor (G-CSF) mobilized peripheral blood was used as a stem cell source. In addition, treatment of animals with PTH(1-34) following transplantation with a limiting number of stem cells markedly improved animal survival and bone marrow cellularity [6]. These data suggest that using PTH to alter activity of the stem cell microenvironment may improve either the yield of stem cells derived from treated donors or the efficiency of engraftment in treated recipients. We hypothesized that similar activities may exist in humans and that PTH may provide a novel means of changing stem cell number and function in settings of clinical importance. The trial detailed here is our first attempt to test the safety of this approach in the context of stem cell donors with cancer who have failed prior efforts at stem cell mobilization.

We performed a Phase I study of PTH at 4 different dose levels, given with filgrastim, to patients with hematologic malignancies who required a second or third mobilization regimen.

PATIENTS AND METHODS

Patients

Patients aged 18 to 75 years with relapsed or refractory Hodgkin's disease or non-Hodgkin's lymphoma, multiple myeloma, or acute myelogenous leukemia (AML) in second or subsequent remission or in first remission with high risk cytogenetics were eligible for this study. Patients were eligible to participate if they did not reach adequate $CD34^+$ cell counts in 1 or 2 prior mobilization attempts, defined as <5 $CD34^+$ cells/μL in the blood or $<2.0 \times 10^6$ CD 34^+ cells/kg after 4 apheresis collections. Patients with serum calcium >10.5 mg/dL or a phosphate level <1.6 mg/dL were excluded. Patients also had to be eligible for transplantation including ECOG performance status of 0, 1, or 2, creatinine <2.0, bilirubin <2.0, ejection fraction $>45\%$, and DLCO $>50\%$ predicted. All subjects signed an informed consent form approved by the Institutional Review Boards of either M.D. Anderson Cancer Center or Dana Farber/Harvard Cancer Center.

Treatment Plan

Treatment with PTH began within 21 days of determination that inadequate $CD34^+$ cells were obtained in the prior mobilization regimen. All subjects received human PTH(1-34) (teriparatide) given as a subcutaneous injection for days 1-14 of the study or until the completion of apheresis. PTH was supplied in multidose pens; subjects were taught the appropriate use, and medication was given at home or in the outpatient clinic, at the following dose levels: 40 μg, 60 μg, 80 μg, and 100 μg a day. Three subjects were treated at each dose level, in ascending order, with an additional 3 subjects to be added for any dose limiting toxicity. Subjects treated with more than 40 μg a day had a daily dose escalation; for example, subjects treated at the 100 μg dose received 40 μg on day 1, 60 μg on day 2, 80 μg on day 3, and then 100 μg on days 4-14. All subjects received filgrastim 10 μg/kg daily on days 10-14 of the study or until the completion of apheresis.

Definitions of Toxicity and Response

Calcium levels, phosphate level, ionized calcium, albumin, blood counts, and vital signs were monitored thrice weekly. On the first day of their maximal PTH dose, subjects were monitored 4 hours after the PTH dose as well. Dose-limiting toxicity was defined as any of the following: serum calcium level >11.5 mg/dL, an ionized calcium level >1.5 mM, systolic blood pressure <80 mmHg, phosphate <1.0 mg/dL. Mobilization was defined as a peripheral $CD34^+$ cell count of >5 cells/μL on day $+14$ of the study. Subjects who met the mobilization criteria proceeded to stem cell collection and, if adequate numbers of stem cells were collected, autologous stem cell transplant. Subjects who did not meet the mobilization criteria were treated off study.

Statistics

Time to neutrophil or platelet engraftment was measured from day 0 of autologous stem cell transplant and was estimated by the Kaplan-Meier method. One subject was censored at day 0 for platelet engraftment as he did not nadir $<20 \times 10^9$/L as a result of transfusion to maintain a platelet count $>40 \times 10^9$/L because of concomitant anticoagulation therapy.

RESULTS

Patient Characteristics

Patient characteristics are outlined in Table 1. Twenty subjects were enrolled on this study. The median age was 57 years with a range of 24-71 years. Thirty-five percent of subjects were male. The majority of subjects (85%) had lymphoma. Fifteen subjects had undergone 1 prior mobilization attempt and 5 subjects had undergone 2 prior mobilization attempts. Eight subjects had received filgrastim mobilization alone, and 12 subjects had received chemotherapy plus filgrastim as their prestudy mobilization regimen. Prior mobilizations regimens included filgrastim alone, cyclophosphamide/filgrastim, rituximab/cyclophospha-