A Phase I Study of Gemtuzumab Ozogamicin (GO) in Combination with Busulfan and Cyclophosphamide (Bu/Cy) and Allogeneic Stem Cell Transplantation in Children with Poor-Risk CD33$^+$ AML: A New Targeted Immunochemotherapy Myeloablative Conditioning (MAC) Regimen

Prakash Satwani,[1] Monica Bhatia,[1] James H. Garvin, Jr.,[1] Diane George,[1] Filemon Dela Cruz,[1] John Le Gall,[1] Zhezhen Jin,[2] Joseph Schwartz,[3] Deirdre Duffy,[4] Carmella van de Ven,[4] Sandra Foley,[4] Ria Hawks,[1] Erin Morris,[4] Lee Ann Baxter-Lowe,[5] Mitchell S. Cairo[4,6,7,8,9]

Children with high-risk acute myelogenous leukemia (AML) (induction failure [IF], refractory relapse [RR], third complete remission [CR3]) have dismal outcomes. Over 80% of AML patients express CD33, a target of gemtuzumab ozogamicin (GO). GO is an active drug in childhood AML but has not been studied in a myeloablative conditioning regimen. We sought to determine the safety of GO in combination with busulfan/cyclophosphamide (Bu/Cy) conditioning before allogeneic hematopoietic stem cell transplantation (alloSCT). GO was administered on day −14 at doses of 3.0, 4.5, 6.0, and 7.5 mg/m^2, busulfan on days −7, −6, −5, −4 (12.8-16.0 mg/kg), and cyclophosphamide on days −3 and −2 (60 mg/kg/day). GVHD prophylaxis consisted of tacrolimus and mycophenolate mofetil. We enrolled 12 patients: 8 IF, 3 RR, 1 CR3; median age: 3 years (1-17); median follow-up: 1379 days (939-2305). Nine received umbilical cord blood (UCB), 2 matched unrelated donors (MUDs) and 1 HLA-matched sibling donor: 3 patients each at GO doses of 3.0, 4.5, 6.0, or 7.5 mg/m^2. No dose-limiting toxicities secondary to GO were observed. Day 100 treatment-related mortality (TRM) was 0%. Myeloid and platelet engraftment was observed in 92% and 75% of patients at median day 22 (12-40) and 42 (21-164), respectively. Median day +30 donor chimerism was 99% (85%-100%). The probability of grade II-IV acute graft-versus-host disease (aGVHD) was 42% and chronic GVHD (cGVHD) was 28%. One-year overall survival (OS) and event-free survival (EFS) was 50% (95% confidence interval [CI], 20.8-73.6). GO combined with Bu/Cy regimen followed by alloSCT is well tolerated in children with poor-risk AML. GO at 7.5 mg/m^2 in combination with Bu/Cy is currently being tested in a phase II study.

Biol Blood Marrow Transplant 18: 324-329 (2012) © *2012 American Society for Blood and Marrow Transplantation*

KEY WORDS: Pediatrics, Gemtuzumab ozogamicin, Allogeneic stem cell transplantation, AML, Conditioning regimen

INTRODUCTION

Acute myelogenous leukemia (AML) is responsible for >30% of all deaths from childhood acute leukemias [1]. The 5-year event-free survival (EFS) rate for childhood AML is approximately 50% [2-4]. The outcome of children with poor-risk AML remains dismal. Michallet et al. [5] analyzed 379 consecutive patients who underwent allogeneic stem cell transplantation (alloSCT) for advanced AML, and Bunin et al. [6] analyzed matched unrelated donors (MUDs) alloSCT for 268 children with AML beyond first remission or refractory to chemotherapy. Both studies suggest that children and adolescents with AML, who are either primary induction failure (PIF), refractory relapse (RR), or in equal to or greater than complete remission

From the [1]Department of Pediatric; [2]Department of Biostatistics; [3]Depatment of Pathology and Cell Biology, New York Presbyterian Morgan Stanley Children's Hospital, Columbia University, New York, New York; [4]Department of Pediatrics, New York Medical College, Valhalla, New York; [5]Department of Surgery, University of California San Francisco, San Francisco, California; [6]Department of Medicine; [7]Department of Pathology; [8]Department of Microbiology and Immunology; and [9]Department of Cell Biology and Anatomy, New York Medical College, Valhalla, New York.

Financial disclosure: See Acknowledgment on page 328.

Correspondence and reprint requests: Mitchell S. Cairo, MD, Marie Fareri Children's Hospital at Westchester Medical Center, New York Medical College, Munger Pavilion Room 110A, Valhalla, New York, 10595 (e-mail: mitchell_cairo@nymc.edu).

Received June 14, 2011; accepted November 1, 2011

1083-8791/$36.00
doi:10.1016/j.bbmt.2011.11.007

(CR)3, are poor risks with an estimated ≤20% disease-free survival following alloSCT. Novel conditioning regimens are needed in this subgroup of poor-risk patients with AML. There have been no studies reported that use gemtuzumab ozogamicin (GO) in combination with myeloablative conditioning (MAC) before alloSCT. We hypothesized that the addition of GO in combination with busulfan/cyclophosphamide (Bu/Cy) MAC followed by alloSCT in children and adolescents with poor-risk $CD33^+$ AML/myelodysplastic syndrome would be safe and well tolerated.

METHODS

Eligibility Criteria

Patients were required to be <21 years of age. Disease-specific requirements included AML-PIF, AML in first, second, or third relapse, or AML ≥CR3. Leukemia cells had to express a minimum of >10% CD33 positivity. Patients who received GO within 30 days before starting conditioning for alloSCT were ineligible. All patients signed an informed consent approved by the institutional review board, and all research protocols were in compliance with the Declaration of Helsinki.

Treatment Plan

Patients received sinusoidal obstruction syndrome (SOS) prophylaxis with enoxaparin sodium on day −15 to day +21. Patients received GO on day −14 intravenously (i.v.) ×1. Bu (i.v.) was administered at a dose of 3.2-4 mg/kg/day divided every 12 hours on day −7 to day −4. On days −3 and −2, patients received cyclophosphamide (60 mg/kg/day). Patients with MUDs and umbilical cord blood (UCB) donors also received rabbit antithymocyte globulin (2 mg/kg/day) from day −5 to day −2.

Patients received GO on day −14 at the dose of 3.0 mg/m^2/dose (dose level 1), 4.5 mg/m^2/dose (dose level 2), 6 mg/m^2/dose (dose level 3), or 7.5 mg/m^2/dose (dose level 4); the dose was assigned at study entry. Starting dose of GO was 3.0 mg/m^2/dose as this dose was tolerated well in combination with other cytotoxic chemotherapy in young adults with AML [7]. The timing of GO administration was based on a half-life of 67 hours [8]. In the absence of pharmacokinetic studies, we anticipated that serum levels of GO would be very low on the day of stem cell infusion as GO would have completed 5 half-lives (335 hours) before day 0. Escalation was planned in groups of 3 subjects with an additional 3 subjects to be added at the first indication of dose-limiting toxicity (DLT). The definition of DLT of GO was either any grade IV nonhematologic toxicity probably or definitely related to GO, any grade III nonhematologic toxicity probably or definitely related to GO that did not resolve in 7 days, or death related to or unresponsive to treatment to severe SOS. The Baltimore criteria were used to assess SOS [9]. DLTs were followed through day +30.

Graft-versus-Host Disease (GVHD) Prophylaxis

Acute GVHD (aGVHD) prophylaxis consisted of tacrolimus, starting on day −1, and mycophenolate mofetil, as we have previously described [10,11]. Patients receiving alloSCT from MUDs received additional methotrexate (5 mg/m^2/dose i.v.) on days +1, +3, +6, and +11. Mycophenolate mofetil taper was stopped on day +60 in patients with more than grade I aGVHD followed by tacrolimus taper over 8 weeks. Acute GVHD and chronic GVHD (cGVHD) were scored according to previously published guidelines [12]. Infection prophylaxis, supportive care, engraftment, chimerism, and HLA typing were performed as per our institutional guidelines [13-16].

Statistics

The product-limit method of Kaplan-Meier was used to determine the probabilities of myeloid and platelet engraftment, aGVHD and cGVHD, relapse, EFS, and overall survival (OS) [17]. EFS was defined as death because of any cause or relapse, and OS was defined as surviving patients with and without leukemia.

RESULTS

Patients Demographic and Disease Status

In this single-center phase I pilot study, 12 patients were enrolled at a median age of 3 years (range: 1-17 years). Median follow-up for surviving patients was 1379 days (range: 939-2305). Sixty-six percent (8 of 12) had induction failure (IF) (7 PIF and 1 reinduction failure), 25% (3 of 12) of patients were transplanted in relapse, and 8% (1 of 12) of patients were transplanted in CR3. Disease status at alloSCT was CR1, 7 of 12 (58%); RR, 3 of 12 (25%); and CR2, 1 of 12 (8%) and CR3 (8%). The complete demographics and key outcome variables are depicted in Table 1.

GO Dose Escalation and Toxicities

Three patients each, at GO doses of 3, 4.5, 6, and 7.5 mg/m^2 were treated.

Patients were monitored for 30 days following alloSCT for nonhematologic toxicity definitely, probably, or possibly related to GO. Two patients had infusion-related fever, and 1 patient had transient grade I hypotension. Five patients had blood stream bacterial infections, of which 3 patients developed clinical sepsis. During the first 30 days following alloSCT, 4 patients developed hyperbilirubinemia (>2 mg/dL), the highest level of bilirubin among this cohort of children was 4.1 mg/dL, 2 patients were diagnosed to have