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Phase I study of dose dense induction and consolidation with gemtuzumab ozogamicin and high dose cytarabine in older adults with AML

Arati V. Rao[a,c,*], *David A. Rizzieri*[a], *Carlos M. DeCastro*[b], *Louis F. Diehl*[b], *Anand S. Lagoo*[d], *Joseph O. Moore*[b], *Jon P. Gockerman*[b]

[a]*Division of Cell Therapy and Bone Marrow Transplantation, Duke Cancer Institute, Durham, NC, USA*
[b]*Division of Medical Oncology, Duke Cancer Institute, Durham, NC, USA*
[c]*Division of Geriatrics, Duke University Medical Center, Durham, NC, USA*
[d]*Division of Hematopathology, Duke University Medical Center, Durham, NC, USA*

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ABSTRACT

Objective: Older adults with acute myeloid leukemia (AML) tend to have worse complete remission (CR) rates and overall survival compared to their younger counterparts. At least one reason for this is increased expression of the multidrug resistance gene (MDR1). Dose dense, high intensity chemotherapy may overcome the MDR1 effect, possibly when combined with anti-CD33 monoclonal antibody gemtuzumab ozogamicin (GO,Mylotarg™), which has been studied in older adults with relapsed AML. This phase I study was aimed at establishing safety by defining a maximum tolerated dose (MTD) by treating older AML patients with two cycles of dose-dense therapy with high dose cytarabine (HiDAC) combined with targeted therapy using GO.

Materials and methods: Nine patients ≥60 years with newly diagnosed, untreated CD33+ AML with adequate renal and hepatic function, and ECOG PS 0-2 were eligible. HiDAC was administered at two dose levels: 3000 mg/m^2 every 12 h for 6 doses (cohort 1), or 9 doses (cohort 2). GO was administered at 6 mg/m^2 on days 1 and 8.

Results: The MTD was HiDAC 3000 mg/m^2 for six doses along with GO 6 mg/m^2. All patients had grades 3–4 pancytopenia, and two patients developed reversible grade 2 neurotoxicity. There were no cases of veno-occlusive disease. Seven of nine patients had a complete response (CR or CRp).

Conclusions: There was no difference in relapse-free survival in our patients when compared to historical data. However, despite high toxicity, two of nine patients treated in this dose-dense fashion remained in CR for >60 months.

* *Corresponding author at:* Box 3961 DUMC, 2400 Pratt St. Suite 9065, Durham NC 27705, USA. Tel.: +1 919 681 0389/681 5185; fax: +1 919 668 1091.
E-mail address: arati.rao@dm.duke.edu (A.V. Rao).

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1. Introduction

The incidence of acute myeloid leukemia (AML) in patients ≥60 years is 17.6 per 100,000 and is expected to increase as the US population ages.[1] Current induction therapy with standard 7+3 regimen results in poor complete remission (CR) rates of 40–50% in older adults with AML.[2] The factors involved in poor response and survival include: high incidence of poor-prognosis karyotypes (5q-, 7q-),[3] high frequency of preceding myelodysplastic syndromes (MDS), and an increased expression of proteins (e.g. MDR1) involved in intrinsic resistance to chemotherapeutic agents.[4] This is compounded by host-related factors, such as poor performance status, comorbidities, and organ function impairment that are a part of the normal aging process. In an attempt to overcome drug resistance and improve survival there have been a few studies in this patient population assessing dose intense therapy with intensive chemotherapy i.e. double induction or increased dose of chemotherapeutic agents, including higher doses of cytarabine provided in a condensed time frame. These studies have resulted in higher CR rates of 50–70%, albeit at the expense of more toxicity.[5–7] More recently, it has been demonstrated in 59 older adults with AML, that a combination of HiDAC (High Dose Cytarabine) at 2 gm/m^2 with daunorubicin 45 mg/m^2 is well tolerated and led to a CR rate of 69%. The 30-day induction mortality was only 10% and median overall survival (OS) was 15.3 months, and the relapse-free survival (RFS) was 13.8 months. Survival for patients who achieved CR was 27 months. Cerebellar toxicities, a significant issue in older patients, occurred in only 7% of patients, and were reversible.[8] Gemtuzumab ozogamicin (GO, Mylotarg™) is a monoclonal antibody to CD33 bound to an anti-tumor antibiotic calicheamicin. At the time of this pilot study, GO was FDA approved for use in treatment of patients with CD33 positive AML in first relapse who are 60 years or older and were not considered candidates for standard cytotoxic therapy.[9] There have been several studies with GO and in a phase I/II CALGB 19902 study, GO has been combined with HiDAC for induction therapy in older adult patients with relapsed/refractory AML. The authors concluded that a single dose of GO 9 mg/m^2 on day 7 after 5 days of HiDAC at 3 gm/m^2 is feasible.[10] It is also noteworthy that while the benefits of post-remission/consolidation therapy have been established in younger AML patients, their utility in older patients continues to be debated.[11] Our aim, thus, was to assess if, in older adults with AML, a dose dense approach to induction therapy with two cycles, without further consolidation therapy, but in combination with immunotherapy using GO might improve the CR rates and relapse-free survival (RFS). This is a report of older adults with AML treated with two cycles of GO and HiDAC as the sole induction and consolidation therapy.

2. Methods

2.1. Patients

Patients≥60 years of age with newly diagnosed, previously untreated CD33+ AML, including secondary AML, were eligible for this pilot study from September 2003 to November 2004. Since patients were being exposed to high doses of cytarabine we ensured that they had adequate renal function (Creatinine≤ 2 mg/dL) and hepatic function, and were ECOG PS 0–2. Patients with acute promyelocytic leukemia i.e. t(15;17), or core-binding factor leukemias i.e. t(8; 21), Inv 16, or t(16;16) were excluded. No active central nervous system (CNS) involvement was allowed. Approval was obtained from the Duke University Medical Center Institutional Review Board and all patients provided written informed consent prior to initiating therapy.

2.2. Treatment plan

This phase I study was aimed at establishing safety by defining a maximum tolerated dose (MTD) in patients treated in a standard 3+3 dose escalation manner. HiDAC was administered in a dose escalation pattern at two dose levels: 3000 mg/m^2 intravenously over one hour, administered every 12 hours for 6 doses (cohort 1), or 9 doses (cohort 2). GO was administered intravenously at 6 mg/m^2 on days 1 and 8 of each cycle for all dose groups. Patients received two cycles of this regimen as sole induction and consolidation therapy. Patients received standard premedication with promethazine, ondansetron, acetaminophen, diphenhydramine and dexamethasone eye drops prior to treatment. All patients received neutrophil growth factor support, transfusions, and antibiotics at the discretion of the treating physician. Patients were assessed for toxicity using standardized CTCAE v3.0 criterion daily post therapy until recovery.[12] A bone marrow (BM) examination for morphology, flow cytometry for leukemia immunophenotyping, and cytogenetics was performed at diagnosis, at the nadir of cycle 1 (11–14 days following the start of therapy), and at the time of count recovery for both cycles (anticipated 4–6 weeks following the start of the cycle).

2.3. Statistical considerations

Our primary endpoint was to assess the maximum tolerated dose (MTD) of a combination of HiDAC and GO. Secondary endpoints included: dose limiting toxicity (DLT), CR rate, and 1-year relapse-free survival (RFS). The statistical design for the phase I trial utilized the traditional 3+3 dose escalation plan.[13] Briefly, the plan was as follows: If 0 out of the first 3 patients enrolled on study experienced DLT, the dose would be escalated to the next level. If one patient experienced DLT of the first 4 then 4 more patients would be entered at the same level. If≤2 of these 8 patients experienced a DLT, then we would escalate to the next cohort. If >1/4 or >2/8 developed a toxicity at a dose level, then we would consider the MTD to be exceeded and the recommended dose for the phase II would be one cohort below this level. The interval between monitoring for toxicity and dose escalation was four weeks.

2.4. Definitions for response and toxicity

Dose limiting toxicity (DLT) was defined as lack of hematopoietic recovery by week 8 following cycle 1 or 2 that was not due to persistent marrow disease. In addition, death within the first 30 days of induction (not related to disease progression) or life-threatening non-hematologic toxicity (cardiac or pulmonary arrest, neurological toxicity) was also considered a DLT. Patient response was evaluated using the guidelines