Original Study

Clofarabine Plus Low-Dose Cytarabine Is as Effective as and Less Toxic Than Intensive Chemotherapy in Elderly AML Patients

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Abstract

We conducted a propensity score-matched comparison of AML patients age ≥ 60 treated with induction chemotherapy by clofarabine plus low dose cytarabine (CLDA) versus idarubicin and cytarabine (IA). There was no statistically significant differences in treatment response, overall survival or early mortality rate between the two induction regimens but CLDA was associated with less toxicities and had longer remission duration.

Introduction: Most patients with acute myeloid leukemia (AML) age ≥ 60 years are not offered intensive induction because of high mortality. Phase 2 studies of clofarabine plus low-dose cytarabine (CLDA) as frontline therapy for elderly AML patients demonstrated high response and acceptable toxicity. **Patients and Methods:** We hypothesized that induction therapy with CLDA provides equivalent outcomes to but is less toxic than intensive induction in these patients. To test this hypothesis, we conducted a propensity score-matched comparison of AML patients age ≥ 60 years given induction CLDA versus idarubicin and cytarabine (IA). Ninety-five patients in both groups were matched according to their propensity score. **Results:** We did not observe statistically significant differences in response, overall survival, or mortality rate between the two induction regimens. However, CLDA produced significantly fewer grade 3 or worse toxicities (46% for CLDA vs. 62% for IA; $P = .03$). Furthermore, among responders, the median response duration was significantly longer with CLDA when we censored patients who underwent stem cell transplantation (15.9 months for CLDA vs. 7.0 months for IA; $P = .033$). **Conclusion:** Compared with intensive induction, CLDA offers equivalent responses and survival but less toxicity in clinically well-matched cohorts of elderly AML patients. Prospective randomized trials to confirm these findings are warranted.

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Introduction

Survival of acute myeloid leukemia (AML) in young patients has improved over the past few decades. However, outcomes of AML in elderly patients remain dismal.[1] One of the challenges in treating AML in elderly patients is that patient and disease characteristics affect the treatment choices and decrease the probability of success. Many measurable and unmeasurable confounding factors influence decision-making for induction therapy in elderly patients, such as comorbidities, patient wishes, performance status, and physician preference. As a result, only a minority of elderly AML patients undergo intensive induction chemotherapy, with the majority of them offered low-intensity therapy such as low-dose cytarabine, 5-azacitidine, and decitabine, mostly with palliative intent.[2,3] Although these low-intensity therapies are well-tolerated and provide a survival benefit over best supportive care, complete remission (CR) is achieved at the best in 25% of the patients, and prolongation of survival is marginal.[4-6]

We previously reported the results of two phase 2 clinical trials investigating the efficacy of frontline therapy with clofarabine plus

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low-dose cytarabine (CLDA) in elderly patients with newly diagnosed AML.[7-9] In these trials, 50% to 60% of the treated patients achieved CR, median overall survival was 11 to 13 months, and the treatment-related mortality rate was 7% to 20%; these findings were comparable with those previously reported with intensive induction chemotherapy in similar patients. We therefore investigated whether patients treated with CLDA, a regimen that is generally better tolerated among older patients, might result in at least equivalent outcomes compared with intensive induction chemotherapy, but perhaps better tolerated. To test this hypothesis, we compared the efficacy, toxicity, and outcomes of patients with newly diagnosed AML who were at least 60 years old treated with CLDA to historical similar patients treated with intensive induction chemotherapy with idarubicin and high-dose cytarabine (IA). Given the intrinsic nature of patient selection bias with the two regimens, we controlled for known pretreatment confounding factors by using propensity score (PS) matching.

Methods

Patients

Seven hundred eighty-eight patients with previously untreated AML who were at least 60 years old and received frontline therapy at The University of Texas MD Anderson Cancer Center from 2002 to 2012 were identified. Of these patients, 192 received induction therapy with CLDA in one of two clinical trials: NCT00088218 (n = 78) and NCT00778375 (n = 114). In comparison, 133 patients received induction therapy with the IA regimen: 45 patients as part of the NCT00422591 trial, and 88 patients outside of the trial. Patients received CLDA treatment between 2004 and 2011, whereas IA treatment was given between 2002 and 2012. Patients who had received prior therapy for antecedent hematological disorders (AHDs), such as hypomethylating agents (HMA) for myelodysplastic syndromes and had progressed to AML were included in the analysis, provided that CLDA or IA was the first therapy for AML. This research protocol was approved by the MD Anderson Institutional Review Board, and the study was conducted in accordance with the Declaration of Helsinki.

Induction Regimens

Details of the 2 clinical trials of the CLDA regimen as frontline therapy for AML in elderly patients were described previously.[7,8] Briefly, patients in the NCT00088218 trial received daily intravenous injections of 30 mg/m^2 clofarabine on days 1 to 5 and once-daily subcutaneous injections of 20 mg/m^2 cytarabine on days 1 to 14. Patients in the NCT00778375 trial received daily intravenous injections of 20 mg/m^2 clofarabine on days 1 to 5 and twice-daily subcutaneous injections of 20 mg cytarabine on days 1 to 10.

All of the patients undergoing the IA regimen received idarubicin 12 mg/m^2 daily on days 1 to 3 and cytarabine 1.5 g/m^2 daily on days 1 to 3.

At least for the first course of induction therapy, all patients were admitted to the hospital and given treatment in a laminar airflow-protected environment. Additionally, all patients received prophylactic antibiotics, antifungals, and antivirals during induction therapy.

Postremission Therapy

The details on the postremission therapy in the 2 CLDA trials were described previously.[7,8] Briefly, in the NCT00088218 trial, patients who had CR alone or CR with insufficient platelet recovery (CRp) received up to 12 cycles of consolidation therapy with attenuated doses of clofarabine and cytarabine (clofarabine 30 mg/m^2 intravenous injection daily on days 1-3 and cytarabine 20 mg/m^2 subcutaneous injections daily on days 1-7). In the NCT00778375 trial, responders received up to 17 cycles of consolidation therapy alternating with attenuated doses of CLDA (clofarabine 20 mg/m^2 intravenous injection daily on days 1-3 and cytarabine 20 mg subcutaneous injections twice-daily on days 1-7) and daily intravenous injections of 20 mg/m^2 decitabine for 5 days in blocks of 3 cycles. Patients whose AML responded to induction IA received up to 6 additional cycles of consolidation therapy with attenuated doses of idarubicin (8 mg/m^2 daily for 2 days) and cytarabine (0.75 g/m^2 daily for 3 days).

Term Definitions

Response to treatment was defined according to the recommendations of the International Working Group.[10] Overall survival (OS) duration was defined as the time from the date of first therapy to that of death or last follow-up, whichever came first. For patients who experienced either CR or CRp, the CR duration was calculated as the time from the beginning of response to therapy to loss of response or death, whichever occurred first.

Statistical Methods

The χ^2 or Fisher exact test was used to assess differences in categorical variables, and the Mann-Whitney *U* test was used to analyze continuous variables. Also, the log-rank test was used to examine between-group differences in OS. The propensity score (PS) for each patient was calculated by conducting multilogistic regression analysis against the type of induction treatment (CLDA vs. IA).[11] Seven dichotomized variables were entered into the multilogistic regression: age ($\geq$ 70 years vs. $<$ 70 years), serum creatinine level ($>$ 1.3 vs. $\leq$ 1.3 mg/dL), serum total bilirubin level ($>$ 1.5 vs. $\leq$ 1.5), bone marrow (BM) blast count ($\geq$ 30% vs. $<$ 30%), cardiac ejection fraction (EF; $>$ 40% vs. $\leq$ 40%), Eastern Cooperative Oncology Group (ECOG) performance status (2-4 vs. 0-1), and Medical Research Council cytogenetic risk (high risk vs. low and intermediate risk).[12] These clinical factors were selected because they likely influence physician's decision-making regarding induction therapy and have been shown to impact treatment outcome of elderly AML patients.[13] We used 70 years as a cut-off for age because previous studies have shown that intensive chemotherapy may not benefit most of the patients with at least age 70 years.[14] Cut-off for creatinine and bilirubin followed the normal upper limit of lab value in our institution. We used 40% as an EF cut-off following the definition of systolic dysfunction in European Society of Cardiology Guidelines.[15] PS matching of the patient cohorts was then conducted using a caliper of 0.25 standard deviation.[16,17] More stringent caliper was tried, but 0.25 gave the best matching model. Statistical analyses were performed using the R statistical programming language

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