ARTICLE

Phase I Clinical Trials in Acute Myeloid Leukemia: 23-Year Experience From Cancer Therapy Evaluation Program of the National Cancer Institute

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Abstract

Background: Therapy for acute myeloid leukemia (AML) has largely remained unchanged, and outcomes are unsatisfactory. We sought to analyze outcomes of AML patients enrolled in phase I studies to determine whether overall response rates (ORR) and mortality rates have changed over time.

Methods: A retrospective analysis was performed on 711 adult AML patients enrolling in 45 phase I clinical trials supported by the Cancer Therapy Evaluation Program of the National Cancer Institute from 1986 to 2009. Changes in ORR and mortality rates for patients enrolled in 1986 to 1990, 1991 to 1995, 1996 to 2000, 2001 to 2005, and 2006 to 2009 were estimated with multivariable logistic regression models. All statistical tests were two-sided.

Results: There was a statistically significant increase in AML patients enrolling in phase I clinical trials over time (1986 to 1990: n = 61; 2006 to 2009: n = 256; P = .03). The ORR for the entire cohort was 15.4% (1986 to 1990: 8.9%, 1991 to 1995: 21.1%, 1996 to 2000: 7.0%, 2001 to 2005: 10.0%, 2006 to 2009: 22.6%), and it statistically significantly improved over time (P < .001). There was a statistically significant improvement in ORRs with novel agents in combination vs single agents (ORR = 22.8% vs 4.7%, respectively, odds ratio = 5.95, 95% confidence interval = 3.22 to 11.9, P < .001). The 60-day mortality rate for the entire cohort was 22.6%, but it statistically significantly improved over time (P = .009).

Conclusions: There has been an encouraging increase in AML patients enrolling in phase I clinical studies over time. The improvement in ORRs appears to be partly because of the increase in combination trials and the inclusion of previously untreated poor-risk AML. Continued enrollment of AML patients in early phase clinical trials is vital for drug development and improvement in therapeutic outcomes.

Over the past four decades, the therapeutic advancements in the management of acute myeloid leukemia (AML) have been minimal. “7+3,” defined as seven days of continuous infusion cytarabine (100–200mg/m²/day) and three days of an anthracycline (most commonly daunorubicin 45–90mg/m²/day), was originally studied in the 1970s by Cancer and Leukemia Group B (CALGB) cooperative group studies and remains the standard induction regimen for all patients younger than 65 to 70 years who can withstand intensive therapy (1-4). For younger AML patients (≤55 years), the complete remission (CR) rate and median overall survival (OS) are approximately 63.9% and 18.8 months, respectively, whereas outcomes are considerably worse in older AML patients (>55 years: CR rates <46.0% and median OS <9 months) (5). A recent European retrospective analysis reviewed overall outcomes in greater than 48 000 AML patients (age 15 years) between 1997 and 2008. A marginal improvement was seen in
five-year OS, from 12.6% in 1997 to 1999 to 14.8% in 2006 to 2008, with no improvement in OS in those age 65 years and older (6).

Excluding all-trans retinoic acid (ATRA) and arsenic trioxide for acute promyelocytic leukemia (APL), no new agents have been approved and incorporated into standard of care for AML since idarubicin was approved in combination (ie, 7+3) in 1990. Induction regimens consisting of idarubicin vs daunorubicin have yielded similar outcomes (7). Gemtuzumab ozogamicin (GO), a monoclonal antibody targeting CD33 antigen linked with calicheamicin, received accelerated approval by the United States Federal Drug Administration (FDA) in 2000 after GO showed efficacy as a single agent in relapsed and refractory AML (8,9). However, GO was withdrawn from the United States market by Pfizer in 2010 after a confirmatory phase III trial revealed toxicity and efficacy concerns (10). A plethora of other new agents with distinct biologic activity have been studied in AML without successful incorporation into standard clinical practice. In 2015, greater than 18,000 patients are expected to be diagnosed with AML, with close to 11,000 deaths in the United States alone, and the incidence of AML is increasing (11,12). New therapies are urgently needed to improve treatment outcomes for these patients.

We retrospectively analyzed outcomes of patients with AML enrolled in National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP)–sponsored phase I clinical trials using the NCI Phase I Clinical Trials Database. Our hypothesis was that outcomes of AML patients enrolled in phase I studies are improving over time as newer and presumably more effective agents are developed.

Methods

Study Design

A retrospective analysis was performed on NCI/CTEP-sponsored phase I clinical studies from 1986 to 2009. The database is maintained by Theradex, an international contract research organization, and is kept up to date by the investigators performing clinical trials and the CTEP of the NCI.

Participants

Sixty-five phase I studies were identified in leukemia, and 45 of these studies principally enrolled AML patients between 1986 to 2009 (Consort Diagram, Figure 1). Adults age 18 years and older with pathologic confirmation of AML were included in the analysis. Clinical and biologic features were analyzed prior to and after enrollment on study. All studies were conducted in accordance with the Declaration of Helsinki and were approved by the ethics committees of each of the participating centers. Informed consent was obtained from each participant for each of the studies reported.

Statistical Analysis

The primary objectives of this analysis were to estimate overall response rates (ORR: CR + partial remission) and all-cause early mortality, defined as death within 30 or 60 days of initiation of therapy, for the whole study and within specific subgroups of patients. CR with incomplete blood count recovery (CRi) was utilized as an ORR criterion after it was incorporated into the International Working Group Response Criteria for AML in 2003 (13). Differences in the rates of mortality and ORR over time were explored by categorizing time into five subgroups roughly divided into five-year increments: 1986 to 1990, 1991 to 1995, 1996 to 2000, 2001 to 2005, and 2006 to 2009. Changes in ORR and mortality rates across these year groups were estimated with multivariable logistic regression models adjusting for patient age, number of prior therapies, and white blood cell count (WBC) at the start of therapy. The overall effect of year group was tested using a Wald test of nested regression models. To determine if the differences in ORR and mortality by year groups was modified by patient age, number of prior therapies, or single-agent vs combination therapy, the corresponding interactions terms were included in the models and retained in the final model if statistically significant ($P < .05$). The average change in the yearly number of patients enrolled was estimated with a simple linear regression model. Differences in patient characteristics were described by Fisher’s exact test with a two-sided $P$ value.

Results

Patient Characteristics

A total of 711 AML patients in 45 phase I clinical trials conducted between 1986 and 2009 were included in this study (Figure 1). Three patients were excluded from the analysis because of insufficient information. No AML patients were enrolled in NCI-sponsored phase I clinical trials during the years 1989, 1994, 1999 and 2004; thus, each subgroup consisted of four years of patient enrollment. As demonstrated in Figure 2, there was a statistically significant increase in AML patients enrolling in phase I clinical trials over time (1986 to 1990: $n = 61$; 2006 to 2009: $n = 256$; slope = 2.3 patients/year, 95% confidence interval [CI] = 0.45 to 4.1, $P = .03$).

Table 1 displays the patient characteristics and clinical outcomes subdivided by dates of enrollment. The median age of the entire patient population was 60 years (range = 18–96), with 51.5% of patients age 60 years and older. The median age of patients that enrolled in phase I clinical trials increased over time from 47 years in 1986 to 1990 to 68 years in 2006 to 2009. The proportion of older patients (≥60 years) that enrolled in these studies increased substantially from 1986 to 1990 (18.0%) to 2006 to 2009 (63.7%). The median number of prior therapies was four (range = 0–29), with 63.3% having three or more prior therapies. However, the proportion of patients with three or more prior therapies decreased over time (1986 to 1990: 68.9%; 2006 to 2009: 54.3%). Accordingly, the most recent cohort (2006 to 2009) had the largest proportion of patients with 0 prior therapies (24.2%), reflecting the incorporation of newly diagnosed poor-risk and/or older age patient populations into phase I trials. Median white blood cell (WBC) count was 3600/mm$^3$ (range = 100–342 800/mm$^3$). Twenty-five out of 45 (55.6%) AML phase I studies were identified as single-agent clinical trials. The proportion of patients enrolling in a single-agent phase I study (40.6% overall) appeared to decrease over time (1986 to 1990: 52.5%; 1991 to 1995: 67.3%; 1996 to 2000: 51.5%; 2001 to 2005: 43.1%; 2006 to 2009: 20.3%), with a reciprocal increase in enrollment to combination studies.

Treatment Outcomes: Response Rates

Forty-two out of 711 (5.9%) patients did not have a response. New therapies are urgently needed to improve treatment outcomes for these patients. Given the high treatment failure rates of AML, the overall effect of year group was tested using a Wald test of nested regression models. To determine if the differences in ORR and mortality by year groups was modified by patient age, number of prior therapies, or single-agent vs combination therapy, the corresponding interactions terms were included in the models and retained in the final model if statistically significant ($P < .05$). The average change in the yearly number of patients enrolled was estimated with a simple linear regression model. Differences in patient characteristics were described by Fisher’s exact test with a two-sided $P$ value.

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No. of studies assessed for eligibility (n=65)  
Excluded* (n=20)

No. of studies enrolling AML and ≥18 years (n=45)

No. of patients enrolled (n=714)  
Excluded from analysis† (n=3)

Assessed for response (n=669)  
Excluded for response assessment‡ (n=42)

**Figure 1.** Sixty-five Cancer Therapy Evaluation Program–sponsored clinical studies enrolled leukemia patients from 1986–2009. Acute myeloid leukemia (AML) patients age 18 years and older enrolled in 45 of these studies. *Patients younger than age 18 years and/or with a diagnosis other than AML were excluded. †Three patients were excluded from analysis given insufficient clinical information. ‡Forty-two patients did not have a response assessment documented and were thus excluded from this analysis. AML = acute myeloid leukemia.

<table>
<thead>
<tr>
<th>No. of AML patients enrolled</th>
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<tr>
<td>N=61</td>
<td>100%</td>
</tr>
<tr>
<td>N=159</td>
<td>95%</td>
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<tr>
<td>N=295</td>
<td>90%</td>
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<tr>
<td>N=455</td>
<td>85%</td>
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<tr>
<td>N=711</td>
<td>80%</td>
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</tbody>
</table>


agent vs combination). As shown in **Figure 3A**, the ORRs for each subgroup were: 1986 to 1990: 8.9% (single agent: 0% vs combination: 19.2%), 1991 to 1995: 21.1% (single agent: 6.2% vs combination: 51.6%), 1996 to 2000: 7.0% (single agent: 1.5% vs combination: 12.5%), 2001 to 2005: 10.0% (single agent: 4.5% vs combination: 14.5%), and 2006 to 2009: 22.6% (single agent: 10.2% vs combination: 25.8%). **Table 2** provides estimates of odds ratios for year subgroup and ORR. While there was a statistical difference in ORR between year groups, particularly an improvement in 2006
to 2009 compared with earlier years ($P < .001$), the difference seems to be largely driven by increased use of combination therapies. When comparing the overall effect of year groups on the probability of response (Supplementary Table 1, available online), there was a statistically significant improvement of ORRs over time in patients younger than age 60 years ($P = .01$) and a nonsignificant trend of improved ORRs in patients age 60 years and older ($P = .10$). Notably, the ORR for those younger than age 60 years and age 60 years and older in 2006 to 2009 ($P = .001$). Finally, there was also a statistically significant improvement in ORR over time in patients treated on combination studies ($P = .03$) but not on single-agent trials ($P = .43$). Test for interaction did not reveal any statistical differences in ORRs between type of study (ie, single agent vs combination) and year group ($P = .51$).

### Treatment Outcomes: Early Mortality

All-cause early mortality was subdivided into 30-day and 60-day mortality rates. The 30-day and 60-day mortality rates for the entire cohort were 11.1% (single agent: 13.8% vs combination: 9.2%) and 22.6% (single agent: 28.0% vs combination: 19.0%), respectively. Thirty-day mortality did not statistically significantly change over time (1986 to 1990: 11.5% vs 2006 to 2009: 8.6%), whereas 60-day mortality rates were statistically significantly higher in earlier years compared with 2006 to 2009 ($P = .009$). Given the apparent improvement in 60-day mortality rates (when compared with 30-day mortality), we analyzed 60-day mortality rates as a function of age, number of prior therapies, and type of clinical study. Figure 4 depicts the 60-day mortality rates among each subgroup for (A) the whole cohort, (B) subdivided by age (<60 vs ≥60 years), (C) subdivided by number of prior therapies (0 vs 1–2 vs ≥3), and (D) subdivided by agents studied (single agent vs combination).

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**Table 1. Patient characteristics**

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<tbody>
<tr>
<td>No. patients enrolled</td>
<td>711</td>
<td>61</td>
<td>98</td>
<td>136</td>
<td>160</td>
<td>256</td>
</tr>
<tr>
<td>No. active studies/no. new studies initiated</td>
<td>45/-</td>
<td>11/-</td>
<td>14/10</td>
<td>11/9</td>
<td>14/11</td>
<td>11/4</td>
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<td>Age, median (range), y</td>
<td>60 (18–96)</td>
<td>47 (18–74)</td>
<td>50 (18–79)</td>
<td>57 (18–76)</td>
<td>65 (20–96)</td>
<td>68 (20–93)</td>
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<td>&lt;60, No. (%)</td>
<td>345 (48.5)</td>
<td>50 (81.9)</td>
<td>71 (72.4)</td>
<td>79 (58.1)</td>
<td>52 (32.5)</td>
<td>93 (36.3)</td>
</tr>
<tr>
<td>≥60, No. (%)</td>
<td>366 (51.5)</td>
<td>11 (18.0)</td>
<td>27 (27.6)</td>
<td>57 (41.9)</td>
<td>108 (67.5)</td>
<td>163 (63.7)</td>
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<tr>
<td>WBC*, median (range)</td>
<td>3.6 (0.1–342.8)</td>
<td>5.8 (0.1–161.5)</td>
<td>3.6 (0.1–342.8)</td>
<td>3.3 (0.1–99.8)</td>
<td>3.3 (0.2–102)</td>
<td>3.5 (0.2–115.3)</td>
</tr>
</tbody>
</table>

*White blood cell count reported as k/mm³. WBC = white blood cell.
number of prior therapies, and (D) type of study (ie, single agent vs combination).

Table 2 provides estimates of odds ratios for year subgroup and 60-day mortality rates. There was a statistically significant improvement in 60-day mortality rates over time \( (P = .009) \). When comparing 60-day mortality rates for patient subgroups by year group (Supplementary Table 1, available online), there was a statistically significant improvement in 60-day mortality rates in patients younger than age 60 years \( (P = .004) \) but not in patients age 60 years and older \( (P = .20) \). However, a test for interaction did not reveal any statistical differences in 60-day mortality rates between age and year group \( (P = .31) \). Similar to ORRs, 60-day mortality rates statistically significantly improved in heavily pretreated patients (ie, ≥3 prior therapies, \( P < .001 \)) but not in patients with zero or one to two prior therapies. Finally, there was an improvement of 60-day mortality rates in the 2006 to 2009 subgroup compared with earlier years in patients treated on combination studies \( (P = .08) \). A test for interaction showed no significant differences between year groups and type of study on the probability of 60-day mortality \( (P = .76) \).

**Discussion**

The persistently poor outcome of AML patients underscores the need for the development and implementation of novel agents. This retrospective analysis of CTEP-sponsored phase I clinical trials demonstrates an increase in the overall enrollment of AML patients on phase I clinical trials over the last 23 years. The concomitant increase in combination studies and inclusion of patients with newly diagnosed AML has been accompanied by an improvement in ORRs and all-cause early mortality rates, with a promising ORR of 22.6% from 2006 to 2009. ORRs were shown to be improving particularly in younger patients (ie, <60 years) and heavily pretreated patients. Although causes of death were not identified in this analysis, early mortality improvements may be partly because of the advances in supportive care and antimicrobial use, rather than a superior safety profile of novel antileukemic agents.

The American Society of Clinical Oncology (ASCO) Policy Statement Update by Weber et al. (14) recently commented on the critical importance of phase I clinical trials in cancer. The primary objective of phase I clinical trials is to define the safety and tolerability of a new drug or treatment regimen and to describe the dose-limiting toxicities observed during dose determination. The majority of phase I clinical trials also evaluate efficacy as a secondary endpoint. Once a tolerable dose and schedule are defined, clinical studies evaluating new oncology agents proceed only if preliminary antitumor activity is demonstrated. Thus, evaluation of response rate as a
secondary endpoint is an important indicator of success in the design of phase I clinical studies. In fact, pembrolizumab and the combination of dabrafenib and trametinib were recently FDA approved for the treatment of melanoma based on the activity seen in the expansion cohorts of phase I trials (15,16).

Response rates are generally low in phase I clinical trials for all cancer subtypes. Horstmann et al. analyzed 460 phase I clinical trials involving 11,935 oncology patients from 1993 to 2002 and reported a stable ORR over time of 10.6%, with an ORR of less than 5% in single-agent phase I clinical studies (17). Estey et al. reported an ORR of 6.4% in leukemia patients enrolling in phase I studies sponsored by the NCI/CTEP from 1974 to 1982 (18). The ORR in AML patients seen on this study (15.4%) appears at least similar to these reports with a 4.7% ORR in single-agent studies vs 22.8% ORR in combination studies. The 2006 to 2009 subgroup in our evaluation enrolled the largest number of patients and had the highest ORR (22.6%) when compared with the other subgroups. Possible explanations for the promising ORR in the most recent cohort are the increased proportion of patients enrolling in combination clinical studies (79.7%) compared with single agents and the inclusion of newly diagnosed and/or non–heavily pretreated patients.

Over the last five years, there have been 23 new therapeutic agents approved by the FDA for hematologic malignancies (chronic myeloid leukemia, n = 5; chronic lymphocytic leukemia, n = 5; lymphomas, n = 5; acute lymphoblastic leukemia, n = 4; multiple myeloma, n = 3; myelofibrosis/polycythemia vera, n = 1). In contrast, no new agents have been approved by the FDA for non-APL AML since 1990, with the exception of GO, which received accelerated approval in 2000 but was withdrawn from the market in 2010 because of safety and efficacy concerns. Limitations in AML drug development include: 1) lack of consistent and standard treatment approaches in AML, which confounds the analyses of OS and disease-free survival endpoints, 2) inherent molecular and clinical heterogeneity of patients with AML, 3) variability in the monitoring and treatment of minimal residual disease, and 4) initial evaluation of new agents restricted to patients with chemoresistant/refractory disease, posing heightened challenges for establishing markers of efficacy in an extremely poor-risk patient population (19,20). Designing and implementing clinical trials in specific subpopulations of AML patients with concomitant pharmacodynamic studies to identify biomarkers of drug sensitivity and response may help to circumvent some of these shortcomings.

Given the underlying complexity in AML pathogenesis and the inherent heterogeneity of the AML population as a whole, sustained single-agent activity is unlikely. Therefore, the investigation of new agents in combination with mechanistically complementary agents should be evaluated early in the drug development process. Precision-targeted approaches to identify patients for specific therapeutic interventions and immunotherapeutic strategies show tremendous promise in cancer. Such approaches should be evaluated early to identify effective combinatorial approaches and to accelerate drug approval in AML. Newly diagnosed poor-risk AML patients, particularly in the elderly population, should be included in early-phase clinical trials to increase the probability of identifying antileukemic activity in a non–heavily pretreated subgroup.

There are currently six active CTEP-sponsored clinical studies in AML patients (Table 3). An additional six phase I and three phase II trials in AML have completed accrual within the past two years. The active studies have a total planned enrollment of 412 patients. Four studies involve complementary combinatorial agents in newly diagnosed untreated patients, while two phase Ib studies examine single-agent ipilimumab in AML patients in CR and relapsed hematologic malignancies post allogeneic stem cell transplantation, respectively.

This is the first comprehensive study to analyze and evaluate outcomes of patients with AML treated on phase I studies, to our knowledge. This analysis was limited to phase I studies in order to comprehensively assess whether outcomes are being improved early in the drug development process. This provides a vantage point to evaluate whether the appropriate patient populations and disease settings are being addressed early in the investigation of novel agents and the changes over time. Nonetheless, our evaluation of AML patients in early-phase clinical trials has limitations that may affect the generalizability of these observations. Given that this analysis focused only on phase I clinical studies, it would be important to compare these results to later-phase clinical trials (ie, phase II and III) to determine whether the same trends and changes are occurring over time. Moreover, these findings relate exclusively to NCI/CTEP-sponsored phase I trials; these results may be disparate when analyzing industry-sponsored or cooperative group studies in AML. Additionally, a limited number of clinical variables were available for our analysis. We did not have access to cytogenetic or molecular abnormalities, types of prior therapies, performance status, or disease-free survival. Secondary AML (treatment related AML or AML preexisting from an antecedent hematologic disorder), a subtype of AML with an extremely poor prognosis, was not predefined in our database. It is likely that secondary AML comprised a substantial proportion of the patient population enrolled in these studies, particularly in the most recent cohorts, as newly diagnosed poor-risk AML patients were increasingly included in the eligibility of phase I studies. Comparing outcomes for de novo AML vs secondary AML would be important in the evaluation of any differences in ORRs and mortality rates on phase I clinical trials in these subsets of patients. Despite these limitations, our findings encompass results from 711 patients enrolled in 45 phase I studies over a 23-year time period. These findings, at least in part, reflect the general trends seen in AML accrual in the United States and clinical outcomes on AML phase I studies over time.

In conclusion, our findings reveal that there has been a statistically significant increase in the enrollment of AML patients on phase I clinical trials over the last 23 years, with improvement in both ORRs and 60-day mortality rates over time. The increasing study of combinations of novel agents, either with established antileukemic cytotoxic drugs or with other investigational agents, in early-phase AML clinical trials has led to an ORR of 22.6% in 2006 to 2009. Early-phase clinical trials should not be the last resort for AML patients. Unfortunately, only 5% to 10% of adult AML patients enroll in clinical trials, and even fewer enroll in phase I studies (21). Educating patients and clinicians about the benefits of early-phase clinical trials is necessary for successful drug development in AML.
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<th>ClinicalTrials.gov identifier</th>
<th>Phase</th>
<th>Protocol title</th>
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<th>Planned accrual</th>
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<td>I</td>
<td>Phase I/IB study of ipilimumab in patients with relapsed hematologic malignancies after allogeneic hematopoietic cell transplantation</td>
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<td>Randomized phase II trial of timed sequential therapy with alvocidib (flavopiridol), Ara-C, and mitoxantrone (FLAM) vs “7 + 3” for adults age 70 years and younger with newly diagnosed AML</td>
<td>Untreated poor-risk AML</td>
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<td>Recently closed to accrual</td>
</tr>
</tbody>
</table>

* Cooperative group studies were excluded. All Cancer Therapy Evaluation Program–sponsored studies in adult acute myeloid leukemia were included if currently recruiting patients (active) or recently closed to accrual within the last two years. AML = acute myeloid leukemia; CTEP = Cancer Therapy Evaluation Program; MEC = mitoxantrone, etoposide, cytarabine; MDS = myelodysplastic syndromes.
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