Time sequential chemotherapy for primary refractory or relapsed adult acute myeloid leukemia: results of the phase II GEMIA protocol

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Background and Objective. High-dose cytarabine (HDAra-C), mitoxantrone and etoposide are the mainstay of several active regimens against relapsed or refractory acute myelogenous leukemia (AML). We designed a phase II study to assess the efficacy and side effects of a time sequential application of mitoxantrone plus intermediate-dose Ara-C followed by HDAra-C plus etoposide (GEMIA) in adult patients with refractory or relapsed AML.

Design and Methods. Patients with refractory or relapsed AML were eligible for GEMIA salvage therapy, which comprised mitoxantrone 12 mg/m²/day on days 1-3, Ara-C 500 mg/m²/day as a 24-hour continuous infusion on days 1-3, followed by HDAra-C 2 g/m²/12-hourly on days 6-8 and etoposide 100 mg/m²/12-hourly on days 6-8. Granulocyte colony-stimulating factor was started on day 14. In patients above the age of 55 the dose of Ara-C in the first sequence (days 1-3) was reduced to 250 mg/m².

Results. Twenty patients were included, of whom 12 achieved complete remission after GEMIA (60%, 95% CI 40-80%), one was refractory and five died early from infection. Two additional patients achieved partial remission after GEMIA and complete remission after consolidation chemotherapy, for a final CR rate of 70% (95% CI 48-88%). Neutrophils recovered at a median of 27 days (range, 22-43) and platelets 46 days (range, 25-59) after the start of treatment. The median duration of remission was 133 days (range, 36-417+) whereas overall survival time lasted for a median of 153 days (range, 13-554+). Treatment-associated toxicity was comprised predominantly of infection, mucositis and diarrhea that reached World Health Organization grades III-IV in 40%, 40% and 30% of patients, respectively. Despite the intention to rapidly proceed to a hematopoietic stem cell transplant in patients in remission, only five patients reached the transplant.

Interpretation and Conclusions. The GEMIA time sequential chemotherapy regimen appears effective in obtaining remissions in refractory and relapsed adult AML. The high toxicity seen, however, suggests that its design is amenable to further improvements, especially in more elderly patients. Since remissions are short-lived, more innovative post-remission strategies are needed.

Key words: acute myeloid leukemia, salvage chemotherapy

In acute myeloid leukemia (AML), relapse or failure to achieve complete remission (CR) with first-line chemotherapy (CT) with an anthracycline plus cytarabine-containing regimen is associated with a very poor short-term prognosis. In these settings salvage regimens which include high-dose cytarabine (HDAra-C), mitoxantrone, idarubicin and/or etoposide may obtain a CR in 40-70% of patients. Patients with primary induction failures and relapses within 6 months from the first CR achieve CR in only 10-30% cases, while those with very late relapses (>2 years) do so in up to 75% Patients who relapse from 6 months to two years have an intermediate chance, around 20-50% of obtaining a second CR depending on the cytogenetic risk group and patient age. However, these CR are short-lived, with nearly all patients relapsing within six months and the median survival being a few months.1,3

Time sequential chemotherapy (TSC) was designed to maximize the number of leukemic cells killed by cytotoxic agents by recruiting cells in the cell cycle using a first sequence of CT, and then administering the second sequence, using cycle-active drugs, at the time of peak cell recruitment induced by the first sequence.6 This approach showed promising results both in relapsed/refractory AML7 and in newly-diagnosed patients.6,8 Based on these results, we designed a novel TSC regimen to be tested in a phase II protocol for high risk relapsed or primary refractory AML. We modified previously described TSC regimens in an effort to improve efficacy. Previous protocols included a first sequence of daunorubicin plus conventional-dose cytarabine (×3 days) and HDAra-C alone in the second sequence (×3 days),6,8 or mitoxantrone plus intermediate-dose cytarabine (×3 days) followed by intermediate-dose cytarabine plus continuous-infusion etoposide (EMA-86 protocol9), with four days of CT-
free interval between cycles. In our GEMIA induction protocol, this interval was shortened to two days, and the second sequence was a modification of the EMA-86 trial, with HD Ara-C and bolus etoposide. Additionally, all patients received granulocyte colony-stimulating factor (G-CSF) to hasten neutrophil recovery.

**Design and Methods**

**Patients’ characteristics**

Twenty adults entered the trial from October 1995 to May 1998. Patients’ characteristics are detailed in Table 1. The median age was 49 years (range 21-64), with 10 men and 10 women. Most patients had unfavorable cytogenetic findings (see Table 1 for details). The FAB subtypes were five M1, five M2, three M4, five M5 and two M6. Nine patients were primary induction failures to first-line chemotherapy, eight were in their first bone marrow relapse < 6 months from first CR (median 3.3 months, range 2-6) and three had relapsed > 6 months (median 26 months, range 16-29). At salvage three patients had pneumonia, while all others were free of active infections.

First-line CT had been the LAM-88 protocol\[^{10}\] in 6 cases and the LAM-94 protocol\[^{11}\] in 14. These protocols include remission-induction CT with daunorubicin (×3 days) or idarubicin (×3 days), 7 days of continuous infusion conventional-dose Ara-C and etoposide (×3 days). Consolidation had consisted of two courses of amascrine and mitoxantrone plus intermediate-dose Ara-C in the LAM-88 and one course of mitoxantrone plus intermediate-dose Ara-C in the LAM-94.

**GEMIA protocol**

The GEMIA salvage induction CT consisted of mitoxantrone 12 mg/m\(^2\)/day on days 1-3, Ara-C 500 mg/m\(^2\)/day as a 24-hour continuous infusion on days 1-3, followed by HD Ara-C 2 g/m\(^2\)/12-hourly on days 6-8 and etoposide 100 mg/m\(^2\)/12-hourly on days 6-8. G-CSF was started on day 14 at 200 µg daily sc and was administered until a stable neutrophil recovery was achieved. In patients above the age of 55 the dose of Ara-C in the first sequence (days 1-3) was reduced to 250 mg/m\(^2\) in an effort to reduce the toxicity of Ara-C in this age group. Dexamethasone eye drops were given from days 1-9 to avoid Ara-C-induced conjunctivitis. Patients were hospitalized throughout treatment in rooms equipped with positive-pressure filtered air and received conventional supportive measures.

Patients who achieved a CR were consolidated with etoposide 100 mg/m\(^2\)/day on days 1-3 and HD Ara-C 2 g/m\(^2\)/day on days 1-5, followed by G-CSF at 5 µg/kg/day sc from day 6. Patients without a sibling donor and who successfully mobilized CD34+ cells to peripheral blood following consolidation CT were to undergo an autologous peripheral blood stem cell transplant (PBSCT) or an allogeneic transplant if a donor was available.

**Definitions and statistics**

Refractory AML was defined as primary induction failure to first-line remission-induction CT or relapse within 6 months from first CR, as defined previously by other authors.\[^{3,12}\] Recurrent AML was defined as first relapse > 6 months from first CR. Achievement of CR was defined as a situation lasting for at least four weeks in which there were <5% blasts in a normocellular bone marrow with >1.5×10\(^9\)/L neutrophils and >50×10\(^9\)/L platelets in peripheral blood and no circulating blasts. The presence of 5-30% blasts in bone marrow was classified as a partial remission (PR), and >30% blasts as no response. Patients who died while aplastic with no blasts in the bone marrow were classified as early death or treatment-related mortality, while patients who died without blood count recovery but had blasts in bone marrow were considered as non-responders. Treatment-related toxicity was graded according to the WHO criteria.\[^{13}\]

The closing date for analysis was September 1, 1998. Overall survival (OS) was calculated from the start of salvage CT until death from any cause or last follow-up for survivors, while remission duration and disease-free survival (DFS) were calculated from CR.

<table>
<thead>
<tr>
<th>Table 1. Patients’ characteristics and response to GEMIA.</th>
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<tbody>
<tr>
<td>No. of patients</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>FAB classification</td>
</tr>
<tr>
<td>Cytogenetics</td>
</tr>
<tr>
<td>Status at GEMIA</td>
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<tr>
<td>Blasts in bone marrow</td>
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<tr>
<td>Leukocytes in peripheral blood</td>
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</table>

\[^{10}\] 2 patients had an 11q23 rearrangement by PCR. \[^{11}\] includes 4 complex karyotypes, 4 abnormal chromosome 7, one +8, 2 rearrangements including 11q23, one inv(3)(q12;p26), one t(9;22), one t(11;15)(q21;q11-12) and one t(6;9)(p23;q34). mo. = months.
Table 2. Outcome of salvage therapy.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>WHO grade (%)</th>
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<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Cutaneous rash</td>
<td>12 (60%)</td>
</tr>
<tr>
<td>Mucositis</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>20 (100%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (35%)</td>
</tr>
<tr>
<td>Hepatic</td>
<td>10 (50%)</td>
</tr>
<tr>
<td>Cerebellar syndrome</td>
<td>18 (90%)</td>
</tr>
<tr>
<td>Fever/infection</td>
<td>-</td>
</tr>
</tbody>
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*one patient died from neutropenic enterocolitis; °includes 4 bacteremias and 8 fevers of unknown origin; #includes 3 cases of pneumonia of unknown origin and one chronic systemic candidiasis; †one patient died from septic shock due to Acinetobacter sp., two from pulmonary aspergillosis and one from pneumonia of unknown origin.

Results

Response to GEMIA

The outcome of this salvage protocol is detailed in Tables 2 and 3. Twelve patients achieved CR after GEMIA (60%, 95% CI 40%-80%). Two additional patients achieved PR after GEMIA and CR after consolidation CT, for a final CR rate of 70% (95% CI 48-88%). Median days (range) from start of chemotherapy to >0.5 \times 10^9/L neutrophils in patients who had hematologic recovery: 27 (22-43); median days (range) from start of chemotherapy to >50 \times 10^9/L in patients who had hematologic recovery: 46 (25-59); median days (range) from start of chemotherapy to neutrophil recovery (> 0.5 \times 10^9/L) occurred on day 46 (range 25-59).

Post-remission therapy and outcome

The non-hematologic toxicity is detailed in Table 3. The main grade 3-4 toxicities were mucositis (40%) and diarrhea (30%). All patients developed neutropenic fever, and eight developed serious infections. Four patients developed pneumonia of unknown origin, which was fatal in one case, and three developed an invasive fungal infection, which was fatal in two cases. Of note, all three patients who entered the study with pneumonia died from pulmonary infection, while none of the other 17 who started CT with no documented infection suffered severe pneumonia. There were two cases of neutropenic enterocolitis, one of which was fatal. Fifteen patients required amphotericin B, 12 empirically and three for a documented mycosis.

Hematologic toxicity
due to neutrophil recovery (>0.5 \times 10^9/L) from the first day of CT was 27 days (range 22-43), while platelet recovery (>50 \times 10^9/L) occurred on day 46 (range 25-59).
mobilized PBSC received an unrelated bone marrow transplant and died on day +140 from extensive chronic graft-versus-host disease.

Discussion

The rate of CR observed with the GEMIA protocol in this phase II trial appears high (60%), especially since most patients were refractory to first-line CT. The sample size is, however, small and thus these preliminary results should be interpreted with caution, although the CR rate appears at least equal to other recently described salvage regimens using these same drugs in novel ways. In the EMA-86 TSC protocol, the CR in 61 refractory patients was 43% with an early death rate of 11%. Kern et al. from Germany tested a novel combination that alternates HD Ara-C with mitoxantrone over 11 days, with a CR rate of 50% in refractory AML. This regimen produces a very prolonged neutropenia (median > 5 weeks) and is associated with a 20-25% early death rate. Toxicity from these intensive salvage CT is significant, with prolonged pancytopenia, frequent severe infectious episodes, high non-hematologic toxicity and early death rates of 10-25%. In this respect, the GEMIA regimen has significant gastrointestinal toxicity, but no other moderate to severe toxicities were observed. When compared with our previous intensive multi-drug salvage regimen which included mitoxantrone plus intermediate dose Ara-C, the incidence of grade 3-4 toxicities and CR rates were similar (54% CR with our previous regimen vs 60% in the GEMIA), although the patient populations differed in the main prognostic factor, that is more refractory patients were treated with GEMIA than in our previous regimen (85% vs 44%, p=0.02).

The CR rate in refractory cases (53%) appeared promising in this trial, especially in early relapsed cases (6 CR in 8 patients). Thus, this regimen may be an adequate option for obtaining significant cytoreduction prior to an allogeneic stem cell transplant, especially if an unrelated donor search is initiated. Mobilization of PBSC was achieved in six out of 9 cases in which it was attempted during recovery from consolidation CT, and this suggests that an autologous PBSC may be offered to most patients with maintained CR if a suitable donor is not available.

All salvage regimens, however, led to remissions that lasted a median of only 3-4 months, thus indicating that a very large leukemic load must remain in vivo despite meeting the definition for CR. Our goal was thus to follow the CR by an autologous or allogeneic SCT within three months from CR to see whether this could lead to longer-lasting remissions. Unfortunately, only five of the 14 patients who achieved remission reached the planned SCT. This large drop-out rate of patients in CR before a planned transplant, mostly due to early relapse, is similar to that found in the experience of relapsed or refractory adult acute lymphoblastic leukemia, in which only 20-30% of eligible patients actually reach the SCT. Other anthracyclines, the platinum analogs and other new chemotherapeutic agents do not appear to give better results than the conventional HD Ara-C combinations, although research in this area must continue.

In summary, the GEMIA salvage regimen appears effective in obtaining high CR rates in refractory and relapsed AML. Toxicity appears to be high, and further dose reductions may be necessary for patients over 55 years old and those with active infections. Rapid relapses are to be expected, and more effective post-remission therapies are urgently needed.

Contributions and Acknowledgments

RM designed the study, was responsible for data management and prepared the manuscript. AA performed the data analysis. RG collaborated in patient care and data management. JS is the head of the Division and participated in writing the paper. AS and SB collaborated in patient care and in preparation of the manuscript.

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Disclosures

Conflict of interest: none.

Redundant publications: data from most patients from the historical control group (ReLAM-88) were reported in a previous manuscript (ref. #15).

Manuscript processing

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References


