Intensive Sequential Chemotherapy With Mitoxantrone and Continuous Infusion Etoposide and Cytarabine for Previously Treated Acute Myelogenous Leukemia

By Eric Archimbaud, Véronique Leblond, Mauricette Michallet, Catherine Cordonnier, Pierre Fenaux, Philippe Travade, François Dreyfus, Jerôme Jaubert, Yves Devaux, and Denis Fiere

Intensive sequential chemotherapy with mitoxantrone, 12 mg/m²/d on days 1 through 3, etoposide, 200 mg/m²/d as a continuous infusion on days 8 through 10, and cytarabine, 500 mg/m²/d as a continuous infusion on days 1 through 3 and 8 through 10 was administered to 72 patients aged less than 60 years with previously treated acute myelogenous leukemia (AML). Forty patients had refractory AML (nonresponse to prior therapy, early first relapse, or multiple relapse) and 32 had late first relapse. Sixty-one percent of patients, with a 95% confidence interval (CI) ranging from 49% to 72%, achieved complete remission (CR), including 45% (CI: 30% to 62%) of refractory patients and 61% (CI: 54% to 93%) of late first relapse patients. Twenty-nine percent of patients (CI: 19% to 41%) did not respond to therapy and 10% (CI: 4% to 19%) died from therapy-related toxicity. Median duration of aplasia was 30 days. Nonhematologic WHO grade 3 or more toxicity included sepsis (57% of patients), vomiting (10%), mucositis (35%), diarrhea (7%), skin rash (6%), and hyperbilirubinemia (11%). Postinduction therapy was attempted in 36 of 44 CR patients: 16 of them received a second course of the same regimen, 7 received maintenance chemotherapy, 4 underwent autologous bone marrow transplantation (BMT), and 9 allogeneic BMT. At a median follow-up of 20 months, 23 of the 44 complete remitters have relapsed, 1 to 14 months after achievement of CR, including 19 of 31 patients not undergoing BMT. Median survival is 7 months with 16% (CI: 4% to 28%) projected survival at 47 months. Median disease-free survival is 6 months with 21% (CI: 3% to 39%) of CR patients projected to remain disease-free at 46 months. Twenty-six percent (CI: 13% to 43%) of the evaluable patients who did not receive transplantation had inversion of CR duration. Among patients younger than 50 years, there was no significant difference in disease-free survival between patients receiving postinduction chemotherapy and those receiving BMT. We conclude that this chemotherapy regimen is highly efficient and could be used as first-line therapy in young patients with AML.

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patients aged less than 60 years were considered for therapy. The six initial patients aged over 60 are not analyzed in this report.

MATERIALS AND METHODS

Patient Eligibility

Patients were eligible for the study if they were younger than 60 years, with a diagnosis of primary AML or AML following transformation of a previously known myelodysplastic syndrome (MDS) or following chemotherapy for a previous malignancy, nonresponsive to chemotherapy, or in first or subsequent relapse. AML was diagnosed according to the revised French-American-British (FAB) Group criteria. Nonresponse to chemotherapy was defined as the absence of CR after at least two courses of intensive anthracycline and cytarabine containing chemotherapy in case of primary AML at diagnosis and one course of intensive chemotherapy in case of secondary AML or primary AML in relapse. Patients with AML following a previous myelodysplastic syndrome were also regarded as nonresponders if they failed to achieve CR after two courses of low-dose cytarabine. Refractoriness was defined, according to Hiddemann et al., as (1) early first relapse, occurring after a first CR of less than 6 months duration or while the patient is still on therapy; and (2) second and subsequent relapses. Late first relapse was defined as first relapse occurring while off-therapy after a first CR of 6 months duration or more. Only patients with a performance status of 2 or less and no grade greater than 2 organ failure according to the World Health Organization (WHO) grading system could enter the study. All patients had to give informed consent according to institutional policy.

EMA Chemotherapy Regimen

The induction phase included two 3-day sequences of chemotherapy separated by a 4-day chemotherapy-free interval. The first sequence associated mitoxantrone, 12/mg/m2/d as a 30-minute intravenous infusion from day 1 to day 3 and cytarabine, 500 mg/m2/d as a continuous infusion on the same days. The second sequence included etoposide, 200 mg/m2/d as a continuous infusion from day 8 to day 10 and cytarabine, 500 mg/m2/d as a continuous infusion on the same days. During induction, 53 patients were monitored in conventional reverse isolation rooms and 19 in sterile laminar air-flow rooms. All patients received gastrointestinal decontamination and prophylactic red blood cells and platelet transfusions. Broad spectrum empirical antibiotherapy was initiated as soon as the patient became febrile.

Postinduction chemotherapy was scheduled to include a second course of the same chemotherapy regimen administered 8 to 12 weeks after initiation of induction chemotherapy. Patients aged less than 50 who had a suitable donor received allogeneic BMT. Some patients aged less than 50 received autologous BMT based on institutional policy to autograft all eligible AML patients in second or subsequent CR. Patients who experienced major complications during the induction phase received maintenance chemotherapy using low-dose cytarabine (for 3 weeks every 6 weeks) until relapse or six monthly courses of the same drugs as used during induction at reduced dosages (mitoxantrone 12 mg/m2 and etoposide 200 mg/m2 on day 1 and cytarabine 80 mg/m2 in days 1 to 5).

Evaluation of Therapy

CR and relapse were defined according to the Cancer and Leukemia Group B (CALGB) criteria. Treatment failures were classified, according to Preisler, as nonresponse (NR), including all patients with proven blastic regrowth even if they died before blood count recovery, and other failures (OF) corresponding to patients who died while nonblastic from presumably chemotherapy-related toxicity. Severity of treatment-related toxicity was graded according to the WHO criteria.

Statistical Analysis

The following parameters were analyzed for potential prognostic significance for CR achievement, disease-free survival (DFS) and overall survival: age, sex, previous therapy, indication for EMA regimen (refractoriness of early first relapse, and primary AML v secondary AML and AML following a previous MDS), WHO performance status, initial hepatosplenomegaly or other extramedullary involvement, fever and hemorrhages, initial blood counts, percent of bone marrow blasts, FAB morphologic subtype, bilirubinemia, serum liver enzymes, and lactate dehydrogenase (LDH) levels.

CR rates were compared using Yate's corrected chi-square, and 95% confidence intervals (CIs) on proportions of CR, NR, and OF patients were calculated using the exact binomial formula. Survival and DFS probabilities were calculated using the Kaplan and Meier product-limit estimate method and their 95% symmetrical CI limit was calculated according to Greenwood's method. Survival curves were compared using the logrank test. For analysis of survival and DFS, patients undergoing autologous or allogeneic BMT while in CR were conventionally censored at the time of transplantation, unless otherwise indicated. Prognostic factors for CR were studied using multiple logistic regression and prognostic factors for DFS and overall survival were studied using Cox's proportional hazard model. All computations were made using BMDP software (BMDP Statistical Software, Los Angeles, CA).

RESULTS

Patient Population

Between April 1986 and April 1990, 72 patients from the eight participating centers entered the study. Accrual by center is indicated in Table 1. All eligible patients seen at the various participating centers since the date of initial participation of each center in the study were included. All entered patients were eligible and subsequently analyzed. Sixty-six patients had primary AML, three patients had AML secondary to chemotherapy for a previous malignancy, and three patients had AML following transformation of a previously known MDS. Overall, 14 patients were nonresponsive to previous chemotherapy and 58 patients had relapsed AML, including 55 patients in first relapse with a median duration of first CR of 9 months (2 to 41 months) and three patients in subsequent relapse (Table 2).

<table>
<thead>
<tr>
<th>Center</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hôpital Edouard Herriot, Lyon</td>
<td>46</td>
</tr>
<tr>
<td>Groupe Hospitalier Pitie-Salpetriere, Paris</td>
<td>11</td>
</tr>
<tr>
<td>Hôpital Albert Michallon, Grenoble</td>
<td>4</td>
</tr>
<tr>
<td>Hôpital Henri Mondor, Créteil</td>
<td>3</td>
</tr>
<tr>
<td>Hôpital Claude Huriez, Lille</td>
<td>3</td>
</tr>
<tr>
<td>Hôpital Nord, Saint-Etienne</td>
<td>2</td>
</tr>
<tr>
<td>Hôpital de l'Hôtel-Dieu, Clermont-Ferrand</td>
<td>2</td>
</tr>
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<td>Hôpital Cochin, Paris</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>72</td>
</tr>
</tbody>
</table>
Among the 14 nonresponsive patients, two patients, with AML after a previous MDS, had previously received two courses of low-dose cytarabine. Seven nonresponsive patients had previously received at least two courses of conventional intensive chemotherapy including 3 days of doxorubicin or daunorubicin at dosages ranging from 35 to 70 mg/m²/d, and 7 to 10 days of cytarabine as a continuous infusion at dosages of 100 or 200 mg/m²/d. Some of these patients had received additional drugs such as 6-thioguanine or CCNU. The remaining five nonresponsive patients had previously received one course of such conventional therapy and one course of high-dose cytarabine (3 g/m²/12 h for 4 days) and amascrine (90 mg/m²/d for 3 days). All the 55 patients treated in first relapse had previously received combinations of the previously described regimens. Overall, 40 of the 72 patients (56%) fulfilled the criteria for refractoriness and 32 (44%) had late first relapse. None of the patients had previously received mitoxantrone or etoposide. Median age of the patients was 42 years (range 16 to 59 years) and initial hematologic characteristics were unremarkable (Table 2).

### Treatment Effectively Received

**Induction.** All patients received the full dose of all three chemotherapeutic agents involved in the induction course, except for one patient with early relapse in whom cytarabine dosage was reduced by 50% due to a reversible cerebellar syndrome complicating a previous course of high-dose cytarabine. One patient, who achieved partial remission after the first induction course, received a second induction course of the same regimen.

**Postinduction.** Among the 44 complete remitters, 16 received a second course of intensive chemotherapy using the same regimen as for induction administered at a median of 9 weeks after initiation of induction (range 8 to 18 weeks) and 4 weeks after achievement of CR. Eight patients received no postinduction therapy because of early relapse (four patients), prolonged aplastic period after the first course (one patient), patient refusal of any further chemotherapy (one patient), or insufficient follow-up (two patients). Seven patients received maintenance chemotherapy using low-dose cytarabine (five patients) or monthly courses of chemotherapy using the same drugs as during induction at reduced dosages (two patients) because of severe toxicity following induction course (four patients) or practical reasons (three patients). Thirteen patients younger than 50 years received BMT within a median of 2 months in CR (range 0.5 to 3.5 months) after conditioning with busulfan and cytoxan or total body irradiation and cytoxan. Four of these patients received autologous BMT according to institutional policy. The remaining nine patients received allogeneic BMT from a family-related donor including six fully matched transplants and three transplants with a one-HLA antigen mismatch.

### Efficacy of Therapy

Results of induction regimen according to the stage of AML at the beginning of therapy are reported in Table 3. Overall, 44 patients or 61% (95% CI ranging from 49% to 72%) achieved CR. One of them reached CR after two courses of chemotherapy while he only had a partial remission after the first induction course. CR rate of nonresponse patients, multiply relapsed patients, and patients in first relapse after a previous CR of less than 6 months duration or while still on therapy were 36%, 33%, and 52%, respectively. Overall, 18 of the 40 patients considered as refractory (45%, CI ranging from 30% to 62%) achieved CR, compared with 26 of the 32 patients in late first relapse (81%, CI ranging from 64% to 93%, $P = .004$). This difference in CR rate was explained by a
higher percentage of NR in refractory patients than in late first-relapse patients (45% v 10%). Overall, 21 patients (29%, CI ranging from 19% to 41%) were nonresponsive and seven patients (10%, CI ranging from 4% to 19%) died of direct toxicity of induction. Four (67%) of the six patients with secondary AML or AML after a previous MDS had NR in refractory patients than in late first-relapse patients (45% v 10%). Overall, 21 patients (29%, CI ranging from 19% to 41%) were nonresponsive and seven patients (10%, CI ranging from 4% to 19%) died of direct toxicity of induction. Four (67%) of the six patients with secondary AML or AML after a previous MDS had nonresponsive NR.

Consolidation while in CR and one prolonged maintenance having received a second course of EMA regimen as a continuing CR for more than 14 months, three of them 45%) at 46 months, respectively. Four patients are in CR and one prolonged maintenance having received a second course of EMA regimen as a continuing CR for more than 14 months, three of them

At a median follow-up of 20 months, 23 patients have relapsed, including 19 of the 31 patients not undergoing BMT, two of the four patients who received allogeneic BMT, and two of the nine patients who received allogeneic BMT. Three of the four CR patients with secondary AML or AML following a previous MDS have relapsed. When patients receiving autologous or allogeneic BMT are censored at the time of transplant, overall survival of the whole group of patients is 16% (CI: 4% to 28%) at 47 months of maximal follow-up, with a median survival of 7 months. DFS of the patients who achieved CR is 21% (CI: 3% to 39%) at 46 months of maximal follow-up, with a median DFS of 6 months. Ten of the 38 patients (26%, CI ranging from 13% to 43%) having a potential follow-up longer than their previous CR and not receiving transplantation had an inversion of CR duration with a subsequent CR longer than the CR preceding EMA chemotherapy. DFS and overall survival of refractory and late first-relapse patients are shown in Figs 1 and 2. Among refractory patients, all patients with previously nonresponsive or multiply relapsed AML have relapsed within 5 months. Overall survival and DFS in this group were 7% (CI: 0% to 19%) at 24 months and 24% (CI: 0% to 52%) at 23 months, respectively. Overall survival and DFS of nonrefractory patients were 28% (CI: 8% to 48%) at 47 months and 23% (CI: 1% to 45%) at 46 months, respectively. Four patients are in continuing CR for more than 14 months, three of them having received a second course of EMA regimen as a consolidation while in CR and one prolonged maintenance with low-dose cytarabine. DFS of the 16 patients who received two courses of intensive chemotherapy is 26% at 46 months. Factors predictive of poor prognosis for CR achievement in the univariate analysis included anemia (P = .003), refractoriness (P = .004), hyperleukocytosis (P = .007), and high serum LDH level (P = .01). In the multivariate analysis, only refractoriness (P = .001), hyperleukocytosis (P = .02), and anemia (P = .05) remained significantly associated with poor prognosis. Although refractory patients had more early relapses than late first-relapse patients, with median DFS of 3.5 months and 8 months, respectively, long-term disease-free survivors were observed in both groups of patients (Fig 1) and the poor prognosis of refractoriness for DFS did not reach statistical significance (P > .1). Poor prognosis factors for survival included elevated serum LDH level (P = .004) and refractoriness (P = .05), with median survival of 4 months and 8 months and long-term survival of 7% and 30%, respectively, in refractory and late first-relapse patients (Fig 2). Only elevated LDH level remained prognostically significant in the multivariate analysis (P = .02). There was no statistically significant difference in CR rate, DFS, and survival between patients treated in the coordinating center and satellite centers nor between patients having received different chemotherapy protocols before entering the study. Projected DFS at 24 months for patients younger than 50
years receiving postinduction therapy with chemotherapy alone, whatever the chemotherapy protocol used, autologous BMT, or allogeneic transplantation are of 34%, 25%, and 39%, respectively. No statistically significant difference is observed at this time between the three groups of patients; however, the numbers of patients in each group are limited.

**Toxicity of EMA 86 Regimen**

Hematologic toxicity of induction included cytopenia with granulocyte count below 0.5 × 10⁹/L during a median of 30 days (range 14 to 59 days) and median platelet transfusion requirement duration of 30 days (range 12 to 85 days). Median time to platelet recovery >100 × 10⁹/L was 47 days (range 25 to 178 days). Extra-hematologic toxicity of induction graded according to the WHO system is shown in Table 4. Major toxicity was infection with severe (grade 3 or more) infectious episodes in 40 patients (57%), including infectious death in nine patients. Four of these patients were blastic at the time of death. Most patients had vomiting, and 25 patients (35%) had severe oral mucositis preventing any food intake for several days. Four patients (6%) had grade 3 or more diarrhea. Eight patients (11%) had marked hyperbilirubinemia without clinical manifestations. Severe bleeding occurred in six patients (8%); four of them died, with persistent blastosis in three. One patient died of a gastric hemorrhage while in CR on the day after his discharge from the hospital and has been considered as a toxic death for analysis. Other toxicities were less frequent; however, one case of severe cerebellar toxicity and two cases of conjunctivitis probably related to cytarabine were observed. The patient who experienced cerebellar toxicity had no cerebellar dysfunction noted during a previous course of high-dose cytarabine. Miscellaneous toxicities included metabolic disorders of unclear origin responsible for the death of one patient, reversible cardiac failure in one patient, and activation of acquired immunodeficiency syndrome in a previously seropositive patient. Overall, 14 patients died during induction, with persistent blastosis as a contributing factor of death in seven of them (Table 4).

Toxicity of the second course of intensive chemotherapy in the selected group of patients who received it was similar to that of the induction course. Median duration of granulocytes below 0.5 × 10⁹/L was 33 days (range 19 to 44 days), median platelet transfusion requirement duration was 33 days (19 to 75 days), and median time of platelet recovery above 100 × 10⁹/L was 71 days (27 to 212 days). Two patients died of infection and one of cerebral hemorrhage.

### Table 4. Extra-Hematologic Toxicity of Induction Chemotherapy

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>WHO Grade (no. of patients)</th>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5*</th>
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</thead>
<tbody>
<tr>
<td>Fever/infection</td>
<td></td>
<td>1</td>
<td>21</td>
<td>10</td>
<td>26</td>
<td>6</td>
<td>9</td>
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<tr>
<td>Nausea/vomiting</td>
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<td>13</td>
<td>45</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>45</td>
<td>12</td>
<td>11</td>
<td>2</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Mucositis</td>
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<td>1</td>
<td>15</td>
<td>25</td>
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<td>0</td>
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<tr>
<td>Cutaneous rash</td>
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<td>7</td>
<td>7</td>
<td>4</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Hyperbilirubinemia</td>
<td></td>
<td>29</td>
<td>32</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Clinical bleeding</td>
<td></td>
<td>60</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>4</td>
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<tr>
<td>Conjunctivitis</td>
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<td>70</td>
<td>2</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>Cerebellar syndrome</td>
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<td>71</td>
<td>0</td>
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<td>1</td>
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<tr>
<td>Cardiac failure</td>
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<td>71</td>
<td>0</td>
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<td>1</td>
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<tr>
<td>Metabolic disorders</td>
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<td>69</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
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</tbody>
</table>

*Overall, 14 patients died during induction chemotherapy. Persisting leukemia was a contributing factor of death in seven of these patients, numbers of patients with persisting leukemia at the time of death are indicated in parentheses.

†Coma of unclear cause.

**DISCUSSION**

Retreatment of patients with previously treated AML with conventional chemotherapy regimens used as first-line therapy induces less than 30% CR in refractory patients and less than 60% CR in late first-relapse patients. Recent approaches to the treatment of these patients generally involved the use of cytarabine in intermediate or high-dose alone or in association with new intercalating agents, such as amascrine, mitoxantrone or idarubicin, etoposide, or aspiraginase. However, reported results with these new regimens widely vary, with CR rates ranging between 0% and 70% because of the limited number of patients included in many reports and because of differences in eligibility criteria and previous therapy received by the patients between the different series. These regimens induce only occasional prolonged CR, and median DFS is generally less than 6 months. Although a direct comparison with already-reported regimens is not possible, our results seem promising with 45% of refractory patients and 81% of late first-relapse patients achieving CR in a series including many patients having previously received high-dose cytarabine. The probability of long-term remission in patients receiving postinduction chemotherapy is above 20% in refractory as well as late first-relapse AML patients. These results seem equivalent to those achieved with autologous and allogeneic BMT in our series as well as in recently reported studies of autologous or allogeneic BMT in
this indication. However, our results regarding long-term DFS and overall survival need to be interpreted cautiously given the limited number of patients with adequate follow-up and the wide CI on the terminal part of the curves.

These encouraging results could be explained by both the choice of drugs and the sequential timing of their administration in EMA regimen. Mitoxantrone is perhaps partially non-cross-reactive with daunorubicin and doxorubicin previously administered in our patients. It has shown superiority over daunorubicin for induction of CR in newly diagnosed AML patients. Etoposide is among the drugs inducing the highest CR rates in phase II trials in AML, following intercalating agents and cytarabine. Furthermore, etoposide and cytarabine have been found synergistic and non-cross-reactive in vitro. Etoposide administered as a continuous infusion in addition to cyclophosphamide induced CR in AML patients nonresponsive to high-dose cytarabine. It has also been shown to increase CR duration when added to a conventional anthracycline-cytarabine regimen in newly diagnosed AML patients. Since the initiation of our study, the association of etoposide and mitoxantrone has demonstrated efficacy in two large series of patients, including one cooperative trial from the Eastern Cooperative Oncology Group (ECOG). Most patients in one of these series were refractory according to the definition used in our study and overall CR rate was 43%; however, no CR lasted longer than 14 months. Association of mitoxantrone, etoposide, and cytarabine in a nonsequential regimen has recently been administered to 36 patients and led to a 58% CR rate, with no CR exceeding 12 months. The usefulness of the sequential design used in this study has been demonstrated by cell-cycle studies showing that the percentage of cells recruited into cycle by the first sequence of chemotherapy was a prognostic factor for achievement of CR. Whether these biologic findings are expressed in the overall clinical results of induction cannot be affirmed in the absence of a randomized study. However, the use of such a sequential therapy has been associated with long CR duration in newly diagnosed patients and could therefore explain the unexpectedly high long-term DFS in our series. The usefulness of the repetition of such a sequential regimen to prolong DFS cannot be evaluated in our series because only a few patients are evaluable for long-term survival. One patient who received maintenance with low-dose cytarabine is alive disease free after more than 3 years in second CR.

Toxicity of EMA regimen remained manageable, with an aplasia duration and death rate similar to those reported in the literature for patients treated with mitoxantrone and etoposide. Higher death rates have been observed in patients treated with high-dose cytarabine in association to mitoxantrone or etoposide, but series are difficult to compare because of the different previous therapies. The limiting extra-hematologic toxicity in our patients was mucositis, as observed in other regimens using etoposide. We observed no unexpected extra-hematologic toxicity in our patients. Initial toxicity did not hinder subsequent autologous or allogeneic BMT: all patients aged less than 50 with a suitable family donor have received allogeneic BMT, and no adverse effect possibly related to the toxicity of previous chemotherapy, such as veno-occlusive disease, was observed after BMT. Repetition of the initial chemotherapy regimen appeared tolerable; however, only 16 patients effectively received the second course of intensive chemotherapy and a bias toward treatment of better-risk patients cannot be ruled out.

Overall, results achieved with this regimen are encouraging for both refractory and late first-relapse AML patients. If recruitment is to play a role in the efficacy of this regimen, association of newly available stimulating factors to chemotherapy might even increase CR rate in refractory patients. Because the CR rate of 81% achieved in late first relapse patients with one course of EMA regimen is at least equal to that achieved in newly diagnosed patients with two courses of conventional chemotherapy, this regimen could probably find a place in the first-line treatment of AML.

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