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# Treatment of Acute Myelogenous Leukemia

## An EBMT-EORTC Retrospective Analysis of Chemotherapy Versus Allogeneic or Autologous Bone Marrow Transplantation

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**Abstract**—*In a retrospective analysis, patients with acute myelogenous leukemia (AML), treated in first complete remission (CR) with chemotherapy or with allogeneic or autologous bone marrow transplantation were compared with respect to their leukemia-free survival from CR. Two hundred and thirty-six patients treated with chemotherapy according to the EORTC AML-5 and AML-6 trials were included. The data of the transplanted patients were taken from two EBMT registries;* 453 *with an allogeneic and* 182 *with an autologous BMT.*

*The very different sources of the data (trials and registries) forced us to be cautious in our conclusions. However, for the patient cohorts analyzed in the present study, BMT patients tended to have a better leukemia-free survival than chemotherapy patients. This was especially the case for the allogeneic BMT after* 6 *months of transplant.*

## INTRODUCTION

THE TREATMENT of patients with acute myelogenous leukemia (AML) consists of two parts: remission induction and prevention of leukemic relapse.

Most investigators agree that intensive induction chemotherapy allows a complete remission (CR) rate of 60–80%. However, there is no consensus about the further optimal therapy to prevent relapse. For the CR patients three main therapeutic options exist:

— chemotherapy, with or without maintenance chemotherapy,
— allogeneic bone marrow transplantation, or
— autologous bone marrow transplantation.

Convincing evidence with respect to this treatment choice could be obtained from prospective randomized trials. Two trials on consolidation chemotherapy versus allogeneic transplantation have been published, using a 'biological randomization' [1, 2]. These studies had conflicting results concerning

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The following centers contributed patients' data for this paper.

*EORTC trials*
Groot Ziekengasthuis, 's-Hertogenbosch; Institut Bordet, Brussels; St. Pierre, Brussels; Hôpital de Bavière, Liège; St. Jan Hospital, Bruges; UZA, Antwerpen; Hôpital de Vervier; Henri Becquerel, Rouen; Centre A. Lacassagne, Nice; Gustave Roussy, Villejuif; Fondation Bergonié, Bordeaux; Hôpital E. Heriot, Lyon; Hôpital Dieu, Paris; Hôpital Bellevue, St. Etienne; RRTI, Rotterdam; St. Radboud Ziekenhuis, Nijmegen; OLV Gasthuis, Amsterdam; AZ, Leiden; Leyenburg, The Hague; Erasmus Universiteit, Rotterdam; Laurentius, Roermond; Akad. Med. Centrum, Amsterdam; Universitätsklinik, Köln; KL Grosshadern, München; Ospedale Maggiore, Milano; Karolinska Sjukh, Stockholm; Centre Hospitalier de Tivoli, Paris; EORTC Data Center, Brussels.

*Allogeneic bone marrow transplants*
Creteil; Genova; Royal Postgraduate Medical School, London; Royal Free Hospital, London; Basel; Huddinge; Westminster Hospital, London; Barcelona University Hospital; Royal Marsden Hospital, London; Hôpital St. Louis, Paris; Leiden—adult; Ulm; Copenhagen; Nijmegen; Helsinki; Besançon; Leiden—pediatric; Hôpital St. Luc, Brussels; Rome; Nancy; Rotterdam; Tübingen; Grenoble; Vienna; Helsinki, pediatric; Santander; Zürich; Pitié Salpetrier, Paris; Lille; Pesaro; Great Ormond Street Hospital, London; Pessac; Marseilles; Nantes; Leuven; Essen; Utrecht; Bologna; Birmingham; Bloomsbury Hospital, London; Geneva; Dublin; Turku; Edinburgh; Milan; Barcelona Hospital S. Creu, S. Pau; St. Etienne; Harley Street Clinic, London; Caen; Berlin; Gotenborg; Hôpital St. Antoine, Paris.

*Autologous bone marrow transplants*
St. Antoine; Bordeaux; Besançon; Nantes; St. Etienne; Marseilles; Tours; Nice; La Pitié; Bloomsbury; Utrecht; Parma; Genova; Rotterdam; Leipzig; Glasgow; Roma; Bern; Nijmegen; Pesaro; Heidelberg; Birmingham; Leiden; Wien; Genève; Ulm; Bologna; Westminster; Pescara; Milano; Pavia; Bolzano; Trieste; Padova; Torino; Cochin; Newcastle; Roma 1; St. Giovanni; Uppsala; Rotondo; Barcelona; Milano 2; Bruxelles; Hôtel Dieu; Vall d'Hebron.

long-term survival. A retrospective analysis using two published series of transplanted patients and a selection of chemotherapy patients from a trial registry has been performed [3]. All studies showed a superiority of bone marrow transplantation (BMT) in preventing leukemic relapse and indicated a trend towards improved survival in the transplant group. However, there was criticism concerning selection bias [2] and lack of statistical power [4].

The present retrospective analysis compares patients with AML in first CR treated subsequently with one of the modalities mentioned above, i.e. chemotherapy or BMT, either allogeneic or autologous. The study was initiated by the European Cooperative Group for Bone Marrow Transplantation (EBMT) and the European Organization for Research and Treatment of Cancer (EORTC). The aim of the study is to explore the evidence with respect to leukemia-free survival (LFS) of the patient cohorts available to us. This exercise was undertaken whilst awaiting further results from randomized trials.

## PATIENTS AND METHODS

A total of eight hundred and seventy-one (871) patients between the ages of 15 and 45 with AML in first CR were analyzed. Two hundred and thirty-six (236) were treated with chemotherapy within the EORTC AML-5 and AML-6 trials [5, 6]. The AML-5 protocol, with 99 patients in the present analysis, was activated in 1976 and last updated in October 1984. The AML-6 trial, with 137 patients in this analysis, was activated in 1983 and the data have been updated until January 1987. Briefly, the AML-5 protocol consisted of an induction treatment of adriamycin on day 1, vincristine on day 2 and cytosine arabinoside every 12 h by push injection on days 3–9. Patients in CR were, after consolidation, randomized to receive different regimens of maintenance therapies for 3 years. The remission induction in the AML-6 trial was by daunorubicin on days 1–3, vincristine on day 2 and cytosine arabinoside every 12 h by push injection on days 1–7. After remission, patients received a consolidation course followed by maintenance therapy (six courses at 6 weeks intervals) with either the same drugs as for induction or a course containing high dose Ara-C. The CR rates turned out to be 63.7% for AML-5 and 67.4% for AML-6.

Six hundred and thirty-five (635) patients were treated with BMT, 453 with allogeneic and 182 with autologous transplantation. The cohorts of transplanted patients were obtained from two EBMT registries, the allogeneic one in Leiden, the Netherlands, and the autologous one in Paris, France. They contain patients transplanted since 1978 and 1982 respectively and were both last updated in January 1987. Earlier reports on their results have been published [7, 8]. The EBMT registries include only transplanted patients and do not collect information concerning induction chemotherapy. In addition, patients who developed a relapse during their waiting time for a considered BMT are not included.

Approximately 50 centers contributed data. The centers were asked to report their consecutive transplantations. However, no auditing procedure was used to check this. Moreover, there was no common treatment protocol, either for induction or for pretransplant treatment, nor for selection criteria to introduce a patient to a BMT program.

In all three groups patient selection was restricted to patients between 15 and 45 years of age. The lower limit was chosen because the chemotherapy trials had this minimal age limit; the upper limit is because allogeneic transplants are generally performed under the age of 45 years.

## STATISTICAL CONSIDERATIONS

In this report we concentrated on LFS from CR. In so doing, we had to make allowance for the fact that BMT patients must have remained in remission from time of CR to time of BMT, while no such requirement held for the chemotherapy group. Trying to avoid this 'time-to-treatment' bias is in our data even more necessary, because of the wide range in time between CR and BMT for the transplanted patients. Methods to cope with this time-to-treatment bias are discussed in Refs. [3, 9]. We followed in principle the method outlined by Mantel and Byar in Ref. [9], and performed additionally a proportional hazards analysis with a time-dependent covariate. First, in a log-rank type analysis we will consider the BMT patients at risk only from their BMT date and not between CR and transplantation; their exposure times are therefore left-truncated. Patients in the chemotherapy group are considered at risk from the date of CR until the latest follow-up. Some patients within the EORTC trials were transplanted later on; these latter patients are considered to be censored at the time of their transplantation.

Starting from CR, at each of the consecutive time points $t_i$, where a relapse or death occurs (so-called 'endpoints' or 'events'), we will compare in a log-rank analysis the number of endpoints among:

— the patients relapse-free alive until $t_i$ in the chemotherapy group and meanwhile not transplanted ($b_i$ endpoints observed at $t_i$ out of $a_i$ patients at risk).

— the patients already transplanted and relapse-free alive until $t_i$ in the allogeneic group ($d_i$ endpoints observed at $t_i$ out of $c_i$ patients at risk).

— similarly in the autologous group ($f_i$ endpoints observed at $t_i$ out of $e_i$ patients at risk).

Thus, under the hypothesis of no difference in the distribution of LFS between the three groups, the expected number of events in the chemotherapy group at time $t_i$ may be computed:

$$E_i^c = a_i(b_i+d_i+f_i)/(a_i+c_i+e_i).$$

In the allogeneic group the expected number of events is

$$E_i^{Allo} = c_i(b_i+d_i+f_i)/(a_i+c_i+e_i).$$

In the autologous group the expected number of events is

$$E_i^{Auto} = e_i(b_i+d_i+f_i)/(a_i+c_i+e_i).$$

Thereafter, the usual log-rank statistic is calculated. In addition to this log-rank analysis, a proportional hazards analysis was performed for the two BMT groups allowing for a different hazard in the first post-transplant period (first 6 months) compared to the second period. Age, sex and year of diagnosis were considered as covariates in this analysis.

The analyses were performed with the SAS package and in particular the PHGLM procedure was used [10].

## RESULTS

The patient characteristics of the three groups are given in Table 1. No important differences existed in age, sex and FAB distribution. Concerning the year of diagnosis, the autologous transplants were mainly performed in the period 1984–1986; this contrasts with the chemotherapy and allogeneic BMT patients which cover the period 1976–1986. A wide range exists between the BMT patients in interval from remission to transplantation; the medians are 16 weeks (allogeneic) and 21 weeks (autologous), respectively. The follow-up is significantly longer for the cohort of allogeneic BMT patients. Results for patients from both AML-5 and AML-6 protocols were pooled because similar results were obtained in terms of LFS (median LFS 50 weeks; 3-years LFS 18%).

The LFS percentages of the chemotherapy patients and the BMT patients cannot be compared directly because of the substantial and highly variable time lag between CR and BMT. The usual log-rank analysis would give a biased result ($\chi^2 = 34$, df = 2, $P \leq 0.001$). The (correct) log-rank analysis, which adjusts for the time from CR to BMT, is given in Table 2. In the analysis the number of patients at risk in each group and the number of patients reaching a relapse or death are considered for each week in which a relapse or death occurs. For descriptive convenience the time intervals in Table 2 are not in weeks but in intervals of 1 month until 24 months and thereafter in intervals of 6 months. The result of the overall log-rank test

*Table 1. Characteristics of the patient cohorts: AML patients in first complete remission*

| | | Chemotherapy | Allogeneic BMT | Autologous BMT |
|---|---|---|---|---|
| | *n* | 236 | 453 | 182 |
| Age (years) | | | | |
| | Mean | 29.6 | 28.0 | 31.5 |
| | S.D. | 8.6 | 7.8 | 8.8 |
| Sex | | | | |
| | male | 113 (48%) | 234 (52%) | 96 (53%) |
| | female | 123 | 219 | 86 |
| FAB | | | | |
| | M1, 2, 3, 6 | 133* (72%) | 314 (69%) | 116 (64%) |
| | M4, 5 | 51* | 139 | 66 |
| Year of diagnosis | | | | |
| 1976–1980 | | 82 (35%) | 81 (18%) | 8 (4%) |
| 1981–1983 | | 71 (30%) | 178 (39%) | 43 (24%) |
| 1984–1986 | | 83 (35%) | 194 (43%) | 131 (72%) |
| Interval from CR to BMT in weeks | | | | |
| 10th percentile | | | 6 | 9 |
| 50th percentile | | | 16 | 21 |
| 90th percentile | | | 36 | 44 |
| Actuarial follow-up in weeks | | | | |
| 10th percentile | | 13 | 44 | 37 |
| 50th percentile | | 108 | 143 | 102 |
| 90th percentile | | 234 | 300+ | 234 |

*Information missing for 52 patients.

*Table 2. Data for the log-rank analysis of the leukemia-free survival (LFS) from complete remission. The BMT patients are left-truncated, i.e. they are not considered to be at risk before their BMT*

| Time (months) | Chemotherapy Number at risk | Chemotherapy Observed endpoints (O) | Chemotherapy Expected endpoints (E) | Allogeneic Number at risk | Allogeneic Observed endpoints (O) | Allogeneic Expected endpoints (E) | Autologous Number at risk | Autologous Observed endpoints (O) | Autologous Expected endpoints (E) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 235 | 3 | 2.3 | 62 | 0 | 0.6 | 10 | 0 | 0.1 |
| 2 | 226 | 7 | 5.7 | 140 | 3 | 3.6 | 28 | 0 | 0.7 |
| 3 | 206 | 8 | 9.6 | 220 | 11 | 10.2 | 47 | 3 | 2.2 |
| 4 | 180 | 13 | 11.9 | 273 | 19 | 18.0 | 77 | 3 | 5.1 |
| 5 | 154 | 7 | 9.2 | 297 | 23 | 17.7 | 103 | 3 | 6.1 |
| 6 | 136 | 14 | 9.8 | 307 | 18 | 22.1 | 113 | 8 | 8.1 |
| 7 | 113 | 12 | 8.9 | 301 | 21 | 23.7 | 119 | 9 | 9.4 |
| 8 | 99 | 4 | 4.0 | 287 | 11 | 11.5 | 113 | 5 | 4.5 |
| 9 | 95 | 2 | 4.1 | 284 | 13 | 12.1 | 113 | 6 | 4.8 |
| 10 | 91 | 6 | 6.6 | 274 | 20 | 19.7 | 106 | 8 | 7.7 |
| 11 | 83 | 6 | 4.0 | 252 | 12 | 12.3 | 96 | 3 | 4.7 |
| 12 | 76 | 5 | 2.0 | 238 | 4 | 6.4 | 95 | 2 | 2.6 |
| 13 | 71 | 3 | 3.4 | 236 | 11 | 11.3 | 91 | 5 | 4.3 |
| 14 | 67 | 5 | 2.3 | 222 | 4 | 7.8 | 83 | 4 | 2.9 |
| 15 | 61 | 2 | 1.9 | 215 | 6 | 6.6 | 80 | 3 | 2.5 |
| 16 | 59 | 4 | 1.9 | 203 | 3 | 6.7 | 73 | 4 | 2.4 |
| 17 | 55 | 2 | 2.1 | 195 | 8 | 7.3 | 68 | 2 | 2.6 |
| 18 | 51 | 0 | 0.3 | 188 | 2 | 1.3 | 63 | 0 | 0.4 |
| 19 | 49 | 2 | 0.8 | 184 | 2 | 3.2 | 62 | 1 | 1.0 |
| 20 | 47 | 2 | 1.6 | 181 | 6 | 6.3 | 60 | 2 | 2.1 |
| 21 | 45 | 1 | 0.3 | 172 | 1 | 1.3 | 57 | 0 | 0.4 |
| 22 | 43 | 2 | 1.1 | 169 | 3 | 4.5 | 53 | 2 | 1.4 |
| 23 | 41 | 1 | 0.3 | 165 | 1 | 1.3 | 51 | 0 | 0.4 |
| 24 | 39 | 0 | 0.3 | 159 | 0 | 1.7 | 50 | 2 | 0.4 |
| 30 | 39 | 2 | 2.6 | 156 | 9 | 10.3 | 46 | 5 | 3.1 |
| 36 | 28 | 6 | 1.4 | 125 | 3 | 6.0 | 33 | 0 | 1.6 |
| 42 | 17 | 3 | 0.5 | 104 | 1 | 2.8 | 24 | 0 | 0.7 |
| 48 | 11 | 1 | 0.3 | 90 | 2 | 2.2 | 21 | 0 | 0.5 |
| Total | | 123 | 99.2 | | 217 | 238.5 | | 80 | 82.7 |

($\chi$ = 6.6, df = 2 and $P$ = 0.036) shows that there are significant differences in LFS between the three groups. Inspection of Table 2 indicates that the significance is mainly due to more observed endpoints in the chemotherapy group than expected under the hypothesis of equal performance of the three therapies.

Performing the same analysis on some other group comparisons led to:

— chemotherapy versus allogeneic and autologous together:
$\chi^2 = 6.2$ df = 1 $P = 0.013$

— chemotherapy versus allogeneic:
$\chi^2 = 6.4$ df = 1 $P = 0.012$

— chemotherapy versus autologous:
$\chi^2 = 3.6$ df = 1 $P = 0.059$

These results indicate that the difference is most pronounced between the chemotherapy and the allogeneic cohorts.

Table 2 also shows, through the number of patients at risk, the fact that the BMT patients are only considered to be at risk from their time of BMT on. The large variation in time interval from CR to BMT (see also Table 1) is reflected in an increasing number of patients at risk in the BMT cohort until 7 months from CR.

Moreover, the log-rank analyses pointed to a significant heterogeneity over time for the differences between observed and expected endpoints. This fits with the substantial early transplant-related mortality in the BMT group. To account for this phenomenon a proportional hazards analysis was done allowing for a different hazard in the first 6 post-transplant months compared to the later post-transplant period. Most of the transplant-related complications occur within the earlier period. The hazards of the allogeneic and autologous group turned out to cross somewhere in the middle of the first 12-month period. The following covariates were originally included in this analysis: age, sex and year of diagnosis (three classes, see Table 1). The analyses showed no significant prognostic influence of these covariates. Therefore, the results in Table 3 are without adjustments. Both BMT groups show slightly better LFS during the first 6 post-transplant months. After 6 months only the

*Table 3. Proportional hazards analysis of chemotherapy as compared to allogeneic and autologous BMT. Leukemia-free survival (in weeks) from complete remission is analyzed*

| | Regression coefficient | *P* | Relative risk* RR | 95% confidence intervals RR |
|---|---|---|---|---|
| Allogeneic BMT vs. chemotherapy, within 6 months of transplant | −0.083 | 0.52 | 0.92 | 0.71–1.19 |
| Allogeneic BMT vs. chemotherapy, after 6 months of transplant | −0.727 | <0.01 | 0.48 | 0.34–0.68 |
| Autologous BMT vs. chemotherapy within 6 months of transplant | −0.262 | 0.13 | 0.77 | 0.54–1.09 |
| Autologous BMT vs. chemotherapy after 6 months of transplant | −0.242 | 0.27 | 0.79 | 0.51–1.21 |

*Risk of relapse or death relative to chemotherapy at equivalent times after first complete remission.

allogeneic BMT group has a significantly better LFS.

## DISCUSSION

A retrospective analysis has always to be considered with caution. In trials such as AML-5 and AML-6 strict inclusion and exclusion criteria are defined. Criteria introducing a patient into a BMT program might be more stringent, and vary from team to team. In our retrospective analysis there is no randomization involved in creating the three treatment groups. There is no common treatment protocol for BMT. Moreover, for both modalities, but especially for chemotherapy, it is clear that views and options concerning present treatment regimens will be slightly different from the treatment applied to the patients analyzed in this study.

This study concerns AML patients in first complete remission. To reach a better comparability of the groups, age at diagnosis is restricted to between 15 and 45 years. The major emphasis in this analysis was put on the statistical methods, in order to perform a less biased analysis. Two measures were taken in line with the methods mentioned in [9].

Patients in the chemotherapy group, who were in some instances transplanted several months after randomization, are censored at time of their transplantation. The patients in the transplantation group are not considered at risk until transplantation. The analysis on these cohorts suggests similar conclusions as found in Refs. [1–3]. LFS over time is better in the allogeneic transplantation group. In contrast to Ref. [1], even in the first half year after transplantation a better, although not significant, performance is observed: we obtained a relative risk of 0.91 (95% confidence interval 0.69–1.21) while Ref. [1] reported 1.35. Our results indicate that despite the transplant-related mortality, the leukemia-free survival is slightly higher for BMT than for chemotherapy shortly after transplantation. Of course, in such a retrospective analysis, explanations are speculative. Recent treatment improvements may have caused the effect. However, also under-reporting to the registry of immediate transplant failures cannot be excluded as (part of) the explanation.

The selection mechanisms leading to the present study cohorts are of course not well circumscribed. The trials had their inclusion and exclusion criteria, apart from AML first CR. But in practice, all eligible patients are seldom entered into the trial by a participating center. For the selection of the BMT patients there is no common protocol, so the selection mechanisms are even less clear. But certainly a series of minimal requirements on the patient's condition is followed by each center.

We found, in line with Refs. [1–3], a trend in favor of BMT. However, it remains desirable to see whether this can be confirmed in a prospective cooperative study, where induction and consolidation therapies are identical in all three treatment groups. The EORTC Leukemia Cooperative Group is currently performing such a study.

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