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# Outcome assessment of age group-specific (±50 years) post-remission consolidation with high-dose cytarabine or bone marrow autograft for adult acute myelogenous leukemia

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## Abstract

***Background and Objective.*** **To assess outcome of an age-adapted post-remission strategy for adult patients with acute myelogenous leukemia (AML, FAB-M3 excluded), including autologous bone marrow transplantation (ABMT) or high-dose cytarabine (HiDAC) consolidation.**

***Design and Methods.*** **AML patients in first complete remission (CR) after doxorubicin-cytarabine-thioguanine (DoxAT) chemotherapy were scheduled to receive two identical early consolidation courses followed by HiDAC (1 g/m²/bd for 6 days), if aged > 50 years, or HiDAC plus total body irradiation (TBI) plus ABMT if aged < 50 years, the bone marrow being harvested prior to the HiDAC/TBI regimen and unpurged. Results were examined by treatment intention and in actual treatment groups, by selected pretreatment and therapy-related variables, and compared with age and disease matched historical patients treated with DoxAT consolidation without additional HiDAC or ABMT.**

***Results.*** **One-hundred and eight (70%) of 153 patients achieved a response and were evaluable after a follow-up of 3.3-8.8 years. According to treatment intention, long-term relapse-free survival (RFS) was significantly improved in both age groups compared with controls (< 50 years: 41% vs 15%, p<0.05; > 50 years: 33% vs 22%, p<0.005). Actually, 41 patients proceeded to ABMT and 24 to the HiDAC cycle (including 5 aged < 50 years), 23 had early consolidation only (1: refusal; 1: inadequate marrow harvest; 21: complications), 10 relapsed and 2 died very early into remission, 7 were submitted to an allogeneic BMT, and one denied any post-remission therapy. The long-term RFS rates for ABMT and HiDAC groups were 53% and 54% (47% for 19 patients aged > 50), respectively, significantly better than for historical patients or those unable to go beyond early consolidation (p<0.005, adjusted for early adverse events). Overall 5-year survival rate was 40% (p<0.0001), 54% for CR patients, 60% after ABMT, and 65% after HiDAC. Relative to the ABMT and HiDAC intensive treatment groups, only the presence of hepatosplenomegaly at diagnosis was associated with a significantly worse outcome like that of the control study.**

***Interpretation and Conclusions.*** **This age-adapted double post-remission consolidation strategy with ABMT (allo-BMT) or HiDAC was applicable to only about two thirds of responders and was effective in about half these cases, regardless of patient age or specific treatment modality. While the loss of CR patients from treatment realization was unrelated to the study design and depended mainly on recurrence of AML and toxic complications, the exact place of ABMT vs HiDAC consolidation remains unsettled, calling for a new study in comparable patient and risk groups.**


Key words: adult AML, high-dose cytarabine, ABMT

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Several recent phase II and phase III clinical trials addressed the issue of post-remission consolidation therapy in adults with acute myelogenous leukemia (AML) in first complete remission (CR). These trials confirmed the therapeutic superiority, over conventional-dose treatments, of high-dose cytarabine (HiDAC), autologous bone marrow transplantation (ABMT), and allogeneic bone marrow transplantation (allo-BMT). Reported relapse-free survival (RFS) rates were 35%-63% with ABMT,[1-6] 31%-66% with allo-BMT.[2,3,6-11] and 27%-52% with HiDAC.[3,7,12-19] In some but not all these studies, exclusion rates from the programmed consolidation phases were reported, ranging from 10%-20%,[13,16,19] to 20%-30%,[5,12] to >30%.[2,3,6,15] This observation alone suggests that the applicability of newer treatment modalities may be even more difficult outside the highly controlled circumstances of clinical trials, especially when high-dose treatments are to be administered to unselected and sometimes critically ill patients. While the real incidence of this insidious phenomenon and its final prognostic implications are undetermined, it is intuitively important to know to what extent innovative study results are reproducible in common clinical practice.

A study conducted from 1984-1987 at Bergamo and Vicenza Hospitals (B/VH, Italy) on a series of unselected, consecutive patients with AML aged 15-60 years showed that, with a short-term therapy (STT)

consisting of a maximum of six total cycles with doxorubicin, conventional-dose cytarabine, and thioguanine (DoxAT), approximately 70% of cases achieved a CR and one fifth of them remained disease-free 5 years later.[20] The best results were obtained in the acute promyelocytic leukemia (APL) subset, with a long-term relapse-free survival rate of 41% ($p<0.05$).[21] In the following five years, APL patients were managed with an all-trans retinoic acid-based protocol, whereas non-APL patients were entered into the BXIII collaborative study with St. Bartholomew's Hospital (SBH, London, UK). The aim of the study was to test the feasibility and value, in patients aged 15-50 years, of ABMT after a HiDAC plus total body irradiation (TBI) myeloablative regimen.[22] At B/VH, patients aged 51-60 years and, therefore, excluded from ABMT, were designated to receive HiDAC only without TBI and ABMT. The final report of this study illustrates, in relation to the above issues, the feasibility and outcome of an age-adapted post-remission strategy including ABMT or HiDAC, as applied to 153 adults with AML (mostly *de novo*, APL excluded) who presented at the two co-operating general hospitals during the study period.

## Materials and Methods

### AML diagnosis

AML was diagnosed according to the revised French-American-British (FAB) system[23] integrated by an immunophenotype study with a panel of monoclonal antibodies for acute leukemia subclassification.[24] Cases with a previously documented myelodysplastic syndrome (MDS) could be included when the bone marrow blast cell content was >30%. Cytogenetic analysis was by means of the conventional Q-banding technique.

### Treatment

This study was conducted from December, 1987 to October, 1993. The outline of the BXIII protocol adopted at B/VH, illustrated in Table 1, contrasted with the previous STT schedule.[20] Briefly, all patients initially responsive to DoxAT induction were consolidated with two similar cycles. Subsequent to this phase, patients still in CR were allocated to 2nd consolidation according to their age. Those aged 15-50 years were to receive HiDAC 1 g/m$^2$/bd for six consecutive days plus TBI and ABMT.[22,25] The autologous bone marrow was harvested from the posterior iliac spines after the first two DoxAT consolidation courses. Marrow mononuclear cells were obtained at a concentration $\geq 2\times10^7$/kg.[26] Patients aged >50 years, electively excluded from ABMT because of uncertainties about the toxicity of the procedure, were scheduled for a single HiDAC course at the same dosage as that in the HiDAC/TBI schedule, with or without additional Dox at the physician's discretion. This treatment was also applicable to younger patients unable to proceed to ABMT. Criteria to submit patients to allogeneic bone marrow transplant (allo-BMT) in first CR were not defined *a priori*. Supportive care measures, infectious disease prophylaxis and treatment and transfusion policy accorded with the institutional protocol in use at the time of treatment.

**Table 1. STT and BXIII treatment regimens in use at B/VH 1984-1993.**

| *Treatment phase* | *STT (1984-1987)* | *BXIII (1987-1993)* |
|---|---|---|
| Induction | DoxAT (x1-2)* | DoxAT (x1-2) |
| Consolidation I | DoxAT (x2-5)° | DoxAT (x2) |
| Consolidation II | | |
| *age 15-50* | – | HiDAC+TBI+ABMT# |
| *age 51-60* | – | HiDAC±Dox |

**Dox, doxorubicin 25 mg/m$^2$/d dd 1-3; A, ara-C 100 mg/m$^2$/bd dd 1-7; T, 6-thioguanine 200 mg/m$^2$/d orally dd 1-7; °All ages; up to 6 total cycles including induction phase. Chemotherapy given at monthly intervals; #HiDAC, ara-C 1 g/m$^2$/bd over 2 h on days 1-6; TBI, 2 Gy/bd dd 7-9; ABMT d 10. ABMT performed within 3-6 months from consolidation I.*

### Definitions

A complete remission (CR) was defined by the following: absent recognizable AML cells in the bone marrow and peripheral blood (myeloblasts and immature monocytic cells <5% in the marrow); normocellular or slightly hypocellular bone marrow with evidence of trilineage hemopoiesis; spontaneous hemoglobin >10 g/dL, neutrophils $>1.5\times10^9$/L, and untransfused platelets $>100\times10^9$/L. A recurrence was defined by the detection of >5% leukemic cells in the bone marrow, or the detection of blast cells in extramedullary sites such as the cerebrospinal fluid, skin etc. CR cases with a successful cytogenetic analysis were subdivided into favorable [t(8;21) and inv(16)], intermediate (normal diploid karyotype, +8, loss of a sexual chromosome), and unfavorable (other karyotypic changes) groups.[27-29] Relapse-free survival (RFS) was the time from the date of CR to recurrence or death in CR. Survival of all patients was calculated from the date of diagnosis to death, and survival from relapse from date of first relapse to death.

### Analysis of results and statistics

Our scope was to evaluate treatment realization and long-term (>5 years) outcome of the BXIII study, in different age and treatment intensity groups, and compare them with those of the previous STT study, in which the cumulative number of post-remission DoxAT courses (Table 1) was not found to affect the probability of RFS.[22] Because treatment realization of the BXIII study was flawed by several drop-outs, outcome was considered first on an intention-to-treat basis and then in actual treatment groups. In

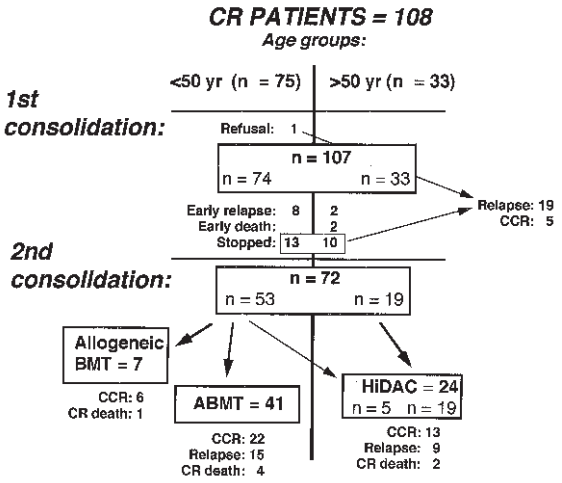


**Figure 1 . Post-remission treatment realization.**

the latter case, because 2nd consolidation was prescribed only to patients who had been in CR for some months, we censored from control groups the patients whose RFS interval was shorter than the median time elapsed from CR to 2nd consolidation in patients who actually received all the planned therapy. This was done to avoid the comparative bias due to very early relapse or death in CR of some patients who were by no means comparable with the full treatment group.[30]

RFS and survival curves were plotted by the Kaplan-Meier method and compared using the log-rank test.[31] The proportions of patients achieving CR and the distribution of selected diagnostic characteristics were compared using the chi-squared test with Yate's correction and, when appropriate, the Student t-test. Significant p values were < 0.05 and trends < 0.1. All calculations were made through the StatWorks™ and StatView+™ software using Apple Macintosh LC475 hardware. Different prognostic groups were identified by intended and received consolidation therapy, number of courses to CR (1 vs >1), interval between day 1 of 1st and 2nd consolidation (< or > the median time observed in each treatment group), additional Dox in the HiDAC course, autologous MNC and CFU-GM (colony forming unit-granulocyte/monocyte) reinfused at ABMT, patient age, blast count, FAB type, cytogenetics, hepatosplenomegaly (liver edge >2 cm below costal margin and/or palpable spleen), and antecedent MDS.

## Results

### Patients and CR rates

The historical STT group consisted of 94 patients of whom 64 achieved a CR (68%). The age, gender, FAB subtype distribution, blast count and incidence of hepatosplenomegaly were similar in these patients to those of BXIII patients (p=n.s.). One hundred and fifty-three consecutive, previously untreated AML patients aged 15-60 years were entered into the BXI-II study. Eighty-six were male. There were 147 cases with a diagnosis of *de novo* AML, and 6 further patients (4%) with AML secondary to MDS or treatment for another neoplastic disease. CR was initially achieved in 108/153 (70%). CR patients were younger than nonresponders (median age 42 vs 46 years, p=0.024) and presented with a lower blast cell count (median 14 vs $21\times10^9$/L, p=0.020). All six patients with FAB-M4eo AML had a positive response. The response rate in other FAB subtypes was as follows: M0 1/3, M1 23/32, M2 34/49, M4 25/35, M5 16/23, M6 3/4, and M7 0/1. Only one patient with secondary AML achieved a CR (17%, p=0.012 vs *de novo* AML). Six patients (13%) died very early during the first course, 3 (7%) succumbed to pancytopenic complications within the first 30 days, 9 (20%) died during a second remission induction attempt, and 27 (60% of nonresponders, 18% of all patients) survived with refractory AML after one or two induction regimens.

### Post-remission treatment

An overview of post-remission treatment realization is depicted in Figure 1. Seventy-four patients younger than 50 years started 1st consolidation and 41 (55%) actually underwent ABMT, after a median of 4.8 months (range 3.3-7.8 months) from CR, and 2.9 months (range 1.4-5.9) from last DoxAT cycle. Seven younger patients (9%) with an HLA-matched donor were submitted to an allo-BMT, 8 relapsed very early (11%) and 18 (24%) were excluded from ABMT because of unresolved infectious complications (n=15), thrombocytopenia (n=1), refusal (n=1), or inadequate bone marrow harvest (n=1); however, 5 of these 18 patients were judged fit enough to receive at least the HiDAC course. Of 33 patients older than 50 years, 2 had an early recurrence (6%), two died very soon of infections (6%), 19 received the planned HiDAC cycle (59%), and 10 could not because of complications and/or very poor performance status (30%). For the 24 total patients receiving HiDAC, the median interval from the last DoxAT course was 1.9 months (range 0.8-3.8), significantly shorter than that for the 41 ABMT patients (p<0.001).

### Relapse-free survival

The minimum follow-up of CR patients in the BXI-II study was 3.3 years. According to intention to-treat, median RFS was 1.47 years and 1.34 years for BXIII and STT patients, respectively, with a 5-8-year rate of 38% and 17% (p<0.1, Figure 2a). When CR patients were stratified by an age below or above 50 years and those undergoing an allo-BMT were censored at time of the transplant, RFS estimates showed that BXIII patients in both age groups had a

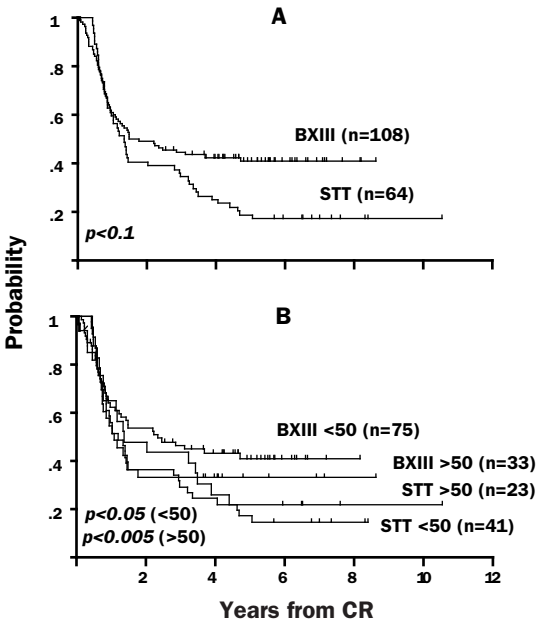


**Figure 2. A: RFS by treatment intention, comparing BXIII and historical STT studies. B: RFS by treatment intention and by age (patients as above).**

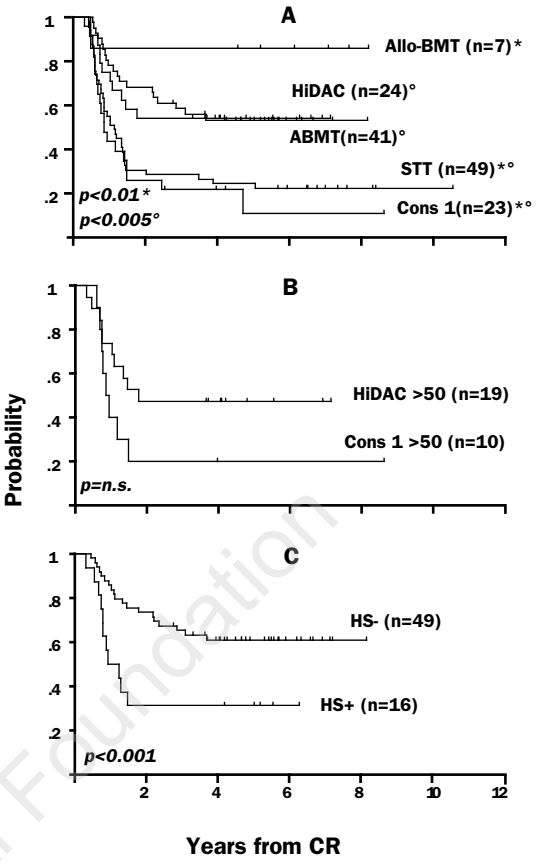


**Figure 3. A: RFS by post-remission treatment, adjusted for early adverse events in STT and Cons 1 groups. Cons 1 denotes BXIII patients stopping therapy at 1st consolidation. B: RFS of HiDAC patients aged >50 years vs. Cons 1 group. C: Cumulative RFS rates of HiDAC/ABMT patients by hepatosplenomegaly (HS±).**

significant prognostic advantage: 2.3 years and 41% vs 1.2 years and 15% ($p<0.05$) for patients aged <50 years; and 1 year and 33% vs 1.3 years and 22% ($p<0.005$) for patients aged >50 years (Figure 2b).

To determine whether this age group-specific improvement was really due to the increased intensity of post-remission therapy, and to specifically assess the contribution of ABMT and HiDAC therapy, we next compared outcome of actual treatment groups excluding from analysis 13 and 15 early drop-outs from the BXIII (Figure 1) and STT studies, respectively, who did not have any chance of receiving 2nd consolidation. The main diagnostic and clinical features of the 95 BXIII patients with a CR duration compatible with the administration of 2nd consolidation are shown in Table 2, divided by treatment actually given and contrasted with 10 early relapse cases. As expected, patients in the HiDAC group were significantly older, and those sent to allo-BMT were younger. Figure 3a and Table 3 report RFS results. Since only a few allo-BMT procedures were carried out and these patients were censored at time of the transplant in the intention-to-treat analysis, it is confirmed that the overall prognostic gain (Figure 2b) was due to 2nd consolidation with either HiDAC or ABMT. In both these groups, the median duration of RFS was not reached by 54% and 53% of the patients, respectively, alive in first CR beyond the fifth year of follow-up. This was not statistically different from the small allo-BMT group (86%), but definitely better than RFS of 49 matched historical STT patients (22% at >5 years) as well as 23 BXIII patients stopping treatment at 1st consolidation for the reasons given above (11% at > 5 years). The RFS of 19 older adults who received HiDAC was 47% (median 1.7 years) (Figure 3b).

### *Relapse and prognostic factors*

As shown before, the diagnostic characteristics of 10 patients suffering from an early recurrence did not differ sensibly from other cases (Table 2). The effect of chromosomal aberrations could be evaluated in 56/108 CR patients (52%) with a successful cytogenetic study (Table 3). According to cytogenetic risk group, the recurrence rate decreased from 60% to 14% (favorable), from 78% to 34% (intermediate), and from 100% to 20% (unfavorable) when 2nd consolidation could be administered. SInce as many as 36.5% (15/41) of ABMT and 37.5% (9/24) of HiDAC-treated patients eventually relapsed, most within 2 years, we looked for other factors able to

**Table 2. Diagnostic features of CR patients by post-remission treatment type.**

| | 1st consolidation only: | | 1st + 2nd consolidation: | | |
|---|---|---|---|---|---|
| | early relapse (n=10) | completed (n=23) | HiDAC (n=24) | ABMT (n=41) | Allo-BMT (n=7) |
| Age (yr), median (range) | 36 (20-59) | 44 (15-59) | 55 (33-60)* | 37 (24-49) | 20 (16-30)° |
| Gender (M/F) | 6/4 | 9/14 | 14/10 | 24/17 | 6/1 |
| FAB M0/1/2/4/5/6 | 0/2/2/3/2/1 | 0/2/8/9/2/2 | 0/6/8/4/6/0 | 1/10/14/12/4/0 | 0/2/2/1/2/0 |
| Blast count (x$10^9$/L), median (range) | 36 (0-230) | 10 (0-113) | 2 (0-171)# | 21 (0-376) | 20 (0-139) |
| Cytogenetics@ (no.), Fv/Int/Ufv | 0/4/0 | 5/5/1 | 2/8/3 | 3/19/2 | 2/2/0 |
| Hepatosplenomegaly, (no.) | 4 | 11 | 6 | 10 | 3 |

**p<0.0001 vs ABMT group, p=0.002 vs 1st consolidation group; °p<0.0001 vs all other groups; #non significant p value vs all other groups; @56 CR patients with successful cytogenetic study. Fv, favorable; Int, intermediate; Ufv, unfavorable.*

**Table 3. DFS by cytogenetics and post-remission treatment intensity.**

| Cytogenetic risk group | No relapses/patients (%) | | | | |
|---|---|---|---|---|---|
| | 1st consolidation | 1st + 2nd consolidation | | | |
| | | HiDAC | ABMT | Allo-BMT | Cumulative |
| Favorable, n=12 | 3/5 (60%) | 0/2 | 1/3 (33%) | 0/2 | 1/7 (14%) |
| Intermediate, n=38 | 7/9 (78%) | 4/8 (50%) | 6/19 (31%) | 0/2 | 10/29 (34%)* |
| Unfavorable, n=6 | 1/1 (100%) | 1/3 (33%) | 0/2 | – | 1/5 (20%) |
| All groups, n=56 | 11/15 (73%) | – | – | – | 12/41 (29%)° |

**p=0.057; °p=0.0078.*



influence RFS duration in the two main treatment groups. Age and presentation blast count (considered as continuous variables with arbitrary cut-off values of 50 years and 10-50×$10^9$/L, respectively), FAB subtype, number of chemotherapy courses to CR (1 vs >1), interval 1st-2nd consolidation (ABMT: ±90 days, HiDAC: ±60 days), additional Dox in the HiDAC course (13 patients), and numbers of MNC (median and range 3.1 and 2.1-6.7 vs 3.2 and 1.8-7.5×$10^7$/kg) and CFU-GM (median and range 1.5 and 0.3-8.3 vs 1.5 and 0.4-4.5×$10^4$/kg) reinfused at ABMT had no significant prognostic effect (p=n.s.). Despite these non significant *p* values from log-rank statistics, partly related to the small numbers of patients in the subgroups, a shorter interval to the HiDAC course and a diagnosis of FAB-M2 or -M5 AML were associated with a 20% or greater RFS improvement, while the absence of hepatosplenomegaly at diagnosis reached the level of statistical significance when, due to superimposable RFS results, HiDAC and ABMT groups were examined together (Table 4 and Figure 3c). Since hepatosplenomegaly was the only significant finding from the univariate comparison of all CR patients receiving 2nd consolidation, a logistic regression analysis was not attempted.

### *Toxicity*

Significant toxic effects observed during induction and 1st consolidation were described previously, and those occurring during ABMT and HiDAC phases are reported in Table 5. The absolute neutropenic and thrombocytopenic period was shorter after HiDAC than ABMT, independently of concurrent Dox given to 13 patients. Both HiDAC-related deaths, however, occurred in patients >50 years who were treated with the Dox-containing regimen. The early complication rate was otherwise very similar between HiDAC and younger ABMT patients in whom there was a toxic death rate of 8% and 7%, respectively. Overall, lethal complications developed in 10 of 108 CR patients (9%), an improvement over the 15% (10/65) remission death rate observed with the previous STT regimen (p=0.022).

### *Survival*

Overall survival of BXIII patients was virtually doubled in comparison with STT patients: median 1.9 vs 0.7 years (p<0.001, Figure 4a). The median survival of 108 patients achieving a CR was 5.8 years, 54% at 5 years and 49% at 8 years (Figure 4b). The improvement was more evident in patients treated intensively with ABMT (60% at 5-8 years) or HiDAC (65% at

**Table 4. RFS by selected prognostic variables.**

| Treatment group | Prognostic variable | No. of pts. | RFS Median (years) | RFS 5-year % |
|---|---|---|---|---|
| HiDAC (time to cycle) | < 60 days | 12 | NR | 67 |
| | > 60 days | 12 | 1 | 42 |
| ABMT+HiDAC | FAB-M2 AML | 22 | NR | 64 |
| | FAB-M5-AML | 10 | NR | 70 |
| | FAB-M1 AML | 16 | 2.21 | 44 |
| | FAB-M4 AML | 16 | 2.7 | 43 |
| | HS + | 16 | 0.9 | 31 |
| | HS – | 49 | NR | 61* |

*NR, not reached; HS: hepatosplenomegaly; *p<0.001 vs hepatosplenomegaly +.*

**Table 5. Comparative short-term toxicity and complications of ABMT and HiDAC phases.**

| | ABMT group* (n=41) | HiDAC group (n=24) |
|---|---|---|
| Days in hospital, median (range) | 30 (18-50) | 28 (23-36) |
| Days with neutrophils < $0.5\times10^9$/L, median (range) | 25 (14-72) | 13 (3-30) p<0.001 |
| Days with platelets < $20\times10^9$/L, median (range) | 38 (15-139) | 13 (3-30) p<0.0001 |
| Documented infections, no. (%): | | |
| *septicemia* | 13 (32) | 9 (37) |
| *bacterial pneumonia* | 11 (27) | 2 (8) |
| *fungal infection* | 4 (10) | 5 (21) |
| Treatment-related deaths,° no. (%) | 3 (7)# | 2 (8)@ |

**ABMT data: median 3.2 (range 1.8-7.5) MNC$x10^7$/kg, median 1.5 (range 0.3-8.3) CFU-GM$x10^4$/kg; °within 100 days from start of ABMT procedure or HiDAC cycle; #including one* C. tropicalis *sepsis, one* Aspergillus spp. *pneumonia and one polymicrobial septicemia; @including one* Aspergillus spp. *sinusitis extending into the brain and one bacterial pneumonia.*

5 years) (Figure 4c).

The proportions of patients alive in first CR were as follows: ABMT 22/41 (54%), HiDAC 13/24 (54%), allo-BMT 6/7 (86%), and 1st consolidation only excluding 10 early relapses and 2 remission deaths 5/23 (22%). Median and 3-year survival from relapse was unrelated to prior treatment intensity: ABMT group 0.6 years and 20%, HiDAC group 1.8 years and 25%, and 1st consolidation only 0.7 years and 26% (p=n.s.). Relapsing patients were retreated with mitoxantrone-etoposide-cytarabine or carboplatin-mitoxantrone-cytarabine combinations. Among 13 patients surviving >2 years from recurrence, 4 underwent an allo-BMT (second transplant in two) and 5 an autograft (second transplant in one).

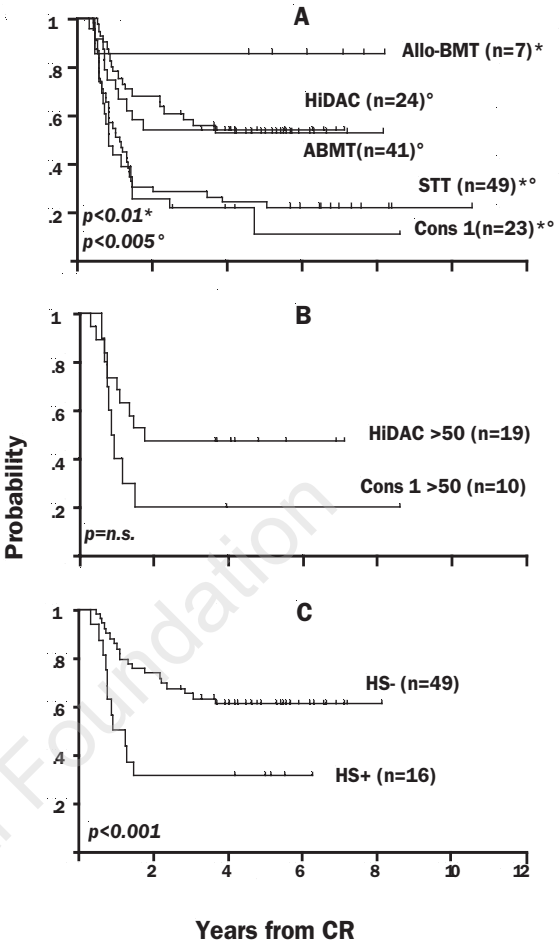


**Figure 4. A: Overall survival of BXIII vs historical STT patients. B: Survival of remitters (CR+) vs nonremitters (CR–) in the BXIII study. C: Survival by actual post-remission treatment in the BXIII study.**

## Discussion

We reviewed the long-term outcome of 108 adult patients with AML in first CR. The planned post-remission treatment of these patients was two induction-like DoxAT courses followed by an ABMT if the patient was younger than 50 years old, or a single HiDAC course if over 50. APL patients with a significantly better outlook were excluded from this study, unmasking the worse prognosis of other AML subtypes.[20,21] With the previous STT regimen the 6-10 years RFS rate was only 17%, regardless of the number of post-remission cycles administered.[22] When the BXIII study began in 1987, ABMT seemed a promising approach to reduce the risk of relapse in younger AML patients in first CR, but the most appropriate context for and feasibility of the treatment were less well defined. This has changed considerably since the definition of the primary prognostic role of cytogenetics[27-29] and drug

resistance mechanisms[32-34] and the maturation of ongoing HiDAC, ABMT, and allo-BMT phase III comparative trials.[2,3,6,8,9,11,15,18,19] These and other phase II studies demonstrated the superiority of these therapeutic measures over conventional treatments but, considered the overlapping RFS figures, the value of allo-BMT as salvage therapy at relapse, and the virtual lack of information on risk-oriented approaches, they also fed persisting uncertainty about the optimal post-remission strategy. Moreover, owing to the increased intensity and toxicity of treatment, the question may arise as to the practical applicability of these schedules in the general patient population.

A first observation from our study was that 36/108 CR patients (33%) were excluded from 2nd consolidation with ABMT or HiDAC for a variety of reasons: early relapse (n=10, 9%), toxic death without relapse (2 patients aged >50 years, 2%), refusal to continue (n=2, 2%), and chemotherapy/disease-related complications (n=22, 20%). Almost invariably, exclusions not caused by recurrence or remission death were associated with a poorer outcome similar to that in the historical STT study. A closely related issue concerned the selection of retrospective control patients treated in the STT study and of BXIII cases given only 1st consolidation. To avoid the comparative bias caused by early drop-outs and to improve the definition of the role of the new strategy beyond treatment intention,[30] we included into analysis only the patients whose RFS was at least comparable to the median interval elapsed from CR to 2nd consolidation in ABMT and HiDAC-treated cases.

The main result was that, in spite of the several problems inherent to treatment realization and the exclusion of very early failures from the control groups, long-term RFS and survival rates argued strongly in favor of the new strategy in both the general intention-to-treat analysis and the actual treatment comparison. The age-based design of the new study allowed direct comparison between HiDAC and ABMT consolidation, albeit in different age groups. After an extended follow-up period of 3.3 to over 8 years, more than half the patients able to receive 2nd consolidation survived disease-free, regardless of treatment type and intensity. Regarding age more specifically, the long-term RFS rate of 19 patients older than 50 years who were able to receive the HiDAC course was 47%, even including two toxic deaths among cases receiving additional Dox. These figures compare well with the 34% RFS rate reported by the *European Bone Marrow Transplant Group* in 111 patients aged >50 years who underwent an ABMT but suffered from a 28% transplant-related mortality.[35] Although ABMT-related toxicity may have been reduced in recent years and the current analysis is limited by the patient number, HiDAC consolidation with 1 g/m$^2$ twice daily for 6 days may thus represent a relatively effective and safe option for this patient subgroup. In keeping with this, other HiDAC studies showed that older adults with AML respond well to the 1.5-2 g/m$^2$ HiDAC dose range (twice daily for up to 6 days) but tolerate badly a 3 g/m$^2$ regimen.[15,19,36,37] Because an intermediate dosage of 0.4-0.5 g/m$^2$ was not shown to be effective,[3,15,38] the preferred HiDAC dose for that particular age group probably lies between 1-2 g/m$^2$ every 12 hours for 5-6 consecutive days, but no study has, as yet, compared the different schedules.

Regarding ABMT and the younger patient population, the 53% RFS plateau at >5 years was in itself a very positive achievement, since APL cases that usually have a better prognosis[20-22] and are exquisitely sensitive to ABMT[39] were excluded. The improved RFS rate of the ABMT group, however, was similar to that of HiDAC-treated patients, a finding that cannot be simply abscribed to small patient numbers or uneven distribution of pretreatment variables, by virtue of the fact that the pattern of recurrent AML and the patients' prognostic profiles, except age, were strikingly similar in the two groups. In the adjusted comparison with control patients (Figure 2a), in fact, the incidence of recurrence over time was almost identical in ABMT and HiDAC groups, as shown by the superimposable course of the early follow-up curve, which also suggests a synergistic effect with the preceding DoxAT therapy. In this sense, pre-ABMT consolidation with at least two chemotherapy courses was the most important factor associated with a continuous CR in another large study,[1] so that we provide some evidence for a similar phenomenon occurring with HiDAC. In contrast, the post-remission administration of only a single HiDAC course was not always associated with a significantly improved outcome.[12,19] If this is so, earlier scheduling of ABMT or the HiDAC cycle in order to achieve the treatment realization rate could increase the risk of relapse. The second analogy between ABMT and HiDAC consolidation concerned risk factors. Limited to the cases examined, outcome was similarly improved in the different cytogenetic risk groups, as in another HiDAC study,[40] while both treatments were doomed to fail in cases with hepatosplenomegaly. This unique diagnostic characteristic, the only one to affect RFS probability in a multivariate analysis of 243 SBH and B/VH AML cases in the STT study,[23] retained its negative clinical significance in the BXIII study. Interestingly, in ABMT patients neither the amount of autologous MNC nor that of CFU-GM correlated with post-graft recurrence rates. All these considerations imply that, for both ABMT and HiDAC-treated patients, the probability of relapse was more likely to be a function of intrinsic disease characteristics rather than of specific treatment modalities.

The conclusions from this study, the long-term results of which are very close to the best therapeutic ranges hitherto reported, may be relevant to the management of older adults with AML, support the concept of double intensification with ABMT or HiDAC at 1 g/m$^2$/dose, and document that, due to the heavy

treatment realization problems encountered, the prognostic benefit derived from this kind of consolidation may not be easily transferrable to the entire patient population. On this basis, paradoxically, any further increase of treatment intensity not compensated for by a concurrent reduction of toxicity carries a definite risk of undertreatment and, ultimately, treatment failure for many patients. Examples were produced in recent years in the neighboring field of adult acute lymphoblastic leukemia.[41,42] Because comparative studies on ABMT vs HiDAC consolidation and on different HiDAC dosages in the diverse age groups may still be warranted, particular attention should be paid to study conditions, realization rate, and interpretative rules. Further progress, in the emerging perspective of a risk-adapted strategy, should be possible by assessing the different treatment options in specific risk classes as defined by age, cytogenetics, drug resistance, and clinical features such as hepatosplenomegaly in this study; and exploiting, in high-risk cases, the therapeutic potential of drug resistance downregulation, regrowth resistance inhibition and induction of autologous graft-versus-leukemia (GvL) effect.[43-45]

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*RB and TB conceived the study design. RB wrote the paper. RR, TL, ADE, MB, and FR were involved in patient management and data collection. TL was involved in data handling and analysis. GB an PB were involved in harvest, separation, and cryopreservation of autologous cells for ABMT. AP was responsible for TBI treatment.*

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### Disclosures

*Conflict of interest: none.*

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### Manuscript processing

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## References

1. Mehta J, Powles R, Singhal S, et al. Autologous bone marrow transplantation for acute myeloid leukemia in first remission: identification of modifiable prognostic factors. Bone Marrow Transplant 1995; 16: 499-506.
2. Lowenberg B, Verdonck LJ, Dekker W, et al. Autologous bone marrow transplantation in acute myeloid leukemia in first remission: results of a Dutch prospective study. J Clin Oncol 1990; 8:287-94.
3. Zittoun RA, Mandelli F, Willemze R, et al. Autologous or allogeneic bone marrow transplantation compared with intensive chemotherapy in acute myelogenous leukemia. N Engl J Med 1995; 332:217-23.
4. McMillan AK, Goldstone AH, Linch DC, et al. High-dose chemotherapy and autologous bone marrow transplantation in acute myeloid leukemia. Blood 1990; 76:480-8.
5. Stein AS, O'Donnell MR, Chai A, et al. *In vivo* purging with high-dose cytarabine followed by high-dose chemo-radiotherapy and reinfusion of unpurged bone marrow for adult acute myelogenous leukemia in first complete remission. J Clin Oncol 1996; 14:2206-16.
6. Sierra J, Brunet S, Granena A, et al. Feasibility and results of bone marrow transplantation after remission induction and intensification chemotherapy in de novo acute myeloid leukemia. J Clin Oncol 1996; 14:1353-63.
7. Cassileth PA, Lynch E, Hines JD, et al. Varying intensity of postremission therapy in acute myeloid leukemia. Blood 1992; 79:1924-30.
8. Schiller GJ, Nimer SD, Territo MC, et al. Bone marrow transplantation versus high-dose cytarabine-based consolidation chemotherapy for acute myelogenous leukemia in first remission. J Clin Oncol 1992; 10:41-6.
9. Gale RP, Buchner T, Zhang M-J, et al. HLA-identical sibling bone marrow transplants vs chemotherapy for acute myelogenous leukemia in first remission. Leukemia 1996; 10:1687-91.
10. Proctor SJ, Taylor PRA, Stark A, et al. Evaluation of the impact of allogeneic transplant in first remission of an unselected population of patients with acute myeloid leukemia aged 15-55 years. Leukemia 1995; 9:1246-51.
11. Reiffers J, Stoppa AM, Attal M, et al. Allogeneic vs autologous stem cell transplantation vs chemotherapy in patients with acute myeloid leukemia in first remission: the BGMT 87 study. Leukemia 1996; 10:1874-82.
12. Phillips GL, Reece DE, Shepherd JD, et al. High-dose cytarabine and daunorubicin induction and post-remission chemotherapy for the treatment of acute myelogenous leukemia in adults. Blood 1991; 77: 1429-35.
13. Harousseau JL, Milpied N, Briere J, et al. Double intensive consolidation chemotherapy in adult acute myeloid leukemia. J Clin Oncol 1991; 9:1432-7.
14. Burke PJ, Karp JE, Geller RB, et al. Cures of leukemia with aggressive post-remission treatment: an update of timed sequential therapy (Ac-D-Ac). Leukemia 1989; 3:692-4.
15. Mayer RJ, Davis RB, Schiffer CA, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia. N Engl J Med 1994; 331:896-903.
16. Preisler HD, Raza A, Early A, et al. Intensive remission consolidation therapy in the treatment of acute nonlymphocytic leukemia. J Clin Oncol 1987; 5:722-30.
17. Wolff SN, Herzig RH, Fay JW, et al. High-dose cytarabine and daunorubicin as consolidation therapy for acute myeloid leukemia in first remission: long-term follow-up and results. J Clin Oncol 1989; 7:1260-7.
18. Bishop JF, Matthews JP, Young GA, et al. A randomized study of high-dose cytarabine in induction in acute myeloid leukemia. Blood 1996; 87:1710-7.
19. Weick JK, Kopecky KJ, Appelbaum FR, et al. A randomized investigation of high-dose versus standard-dose cytosine arabinoside with daunorubicin in

patients with previously untreated acute myeloid leukemia: A southwest Oncology group study. Blood 1996; 88:2841-51.
20. Battista R, Bassan R, D'Emilio A, et al. Short-term remission induction and consolidation therapy for adult acute myelogenous leukaemia. Hematol Oncol 1991; 9:43-52.
21. Bassan R, Battista R, Viero P, et al. Short-term treatment for adult hypergranular and microgranular acute promyelocytic leukemia. Leukemia 1995; 9:238-43.
22. Rohatiner AZS, Battista R, Bassan R, et al. Short term therapy (STT) for acute myelogenous leukaemia (AML). Leukemia 1992; 6 (Suppl 2):85-8.
23. Bennett JM, Catovsky D, Daniel M-T, et al. Proposed revised criteria for the classification of acute myeloid leukemia. A report of the French-American-British Cooperative Group. Ann Intern Med 1985; 103:620-5.
24. Bassan R, Rambaldi A, Viero P, et al. Integrated use of morphology, cytochemistry, and immune marker analysis to identify acute leukaemia subtypes. Haematologica 1989; 74:487-90.
25. AZS Rohatiner, Bassan R, Raimondi R, et al. Myeloablative therapy with autologous bone marrow transplantation (ABMT) as consolidation of first remission in younger patients with acute myelogenous leukaemia (AML) [abstract]. Br J Haematol 1996; 93 (Suppl 2): 225. n. 848.
26. Gilmore MJML, Prentice HG, Blacklock HA, et al. A technique for rapid isolation of bone marrow mononuclear cells using Ficoll-Metrizoate and the IBM 2991 blood cell processor. Br J Haematol 1982; 50:619-26.
27. Keating MJ, Smith TL, Kantarjian H, et al. Cytogenetic pattern in acute myelogenous leukemia: a major reproducible determinant of outcome. Leukemia 1988; 2:403-12.
28. Dastugue N, Payen C, Lafage-Pochilatoff M, et al. Prognostic significance of karyotype in *de novo* adult acute myeloid leukemia. Leukemia 1995; 9:1491-8.
29. Grimwade D, Walker H, Harrison C, et al. Impact of diagnostic cytogenetics on outcome in AML: analysis of 1,613 patients entered into the UK MRC AML 10 trial [abstract]. Blood 1996; (Suppl 1):634a. n. 2525.
30. Miggiano MC, Gherlinzoni F, Rosti G, et al. Autologous bone marrow transplantation in late first complete remission improves outcome in acute myelogenous leukemia. Leukemia 1996; 10:402-9.
31. Peto R, Pike MC, Armitage P, et al. Design of analysis of randomised clinical trials requiring prolonged observation of each patient. Br J Cancer 1977; 35:1-39.
32. te Boekhorst PAW, Lowenberg B, van Kapel J, et al. Multidrug resistant cells with high proliferative capacity determine response to therapy in acute myeloid leukemia. Leukemia 1995; 9:1025-31.
33. Del Poeta G, Stasi R, Aronica G, et al. Clinical relevance of P-glycoprotein expression in de novo acute myeloid leukemia. Blood 1996; 87:1997-2004.
34. List AF, Spier CS, Grogan TM, et al. Overexpression of the major vault transporter protein lung-resistance protein predicts treatment outcome in acute myeloid leukemia. Blood 1996; 87:2464-9.
35. Cahn JY, Labopin M, Mandelli F, et al. Autologous bone marrow trasplantation for first remission acute myeloblastic leukemia in patients older than 50 years: a retrospective analysis of the European Bone Marrow Transplant Group. Blood 1995; 85:575-9.
36. Herzig RH. High-dose ara-C in older adults with acute leukemia. Leukemia 1996; 10 (Suppl 1):S10-1.
37. Schiller GJ. Post-remission therapy of acute myeloid leukemia in older adults. Leukemia 1996; 10 (Suppl 1):S18-20.
38. Schiller G, Nimer S, Gajewsky J, et al. Effect of induction cytarabine dose intensity on long-term survival in acute myelogenous leukemia: results of a randomized, controlled study. Leuk Lymphoma 1993; 11:69-77.
39. Linker CA, Ries CA, Damon LE, et al. Autologous bone marrow transplantation for acute myeloid leukemia using busulfan plus etoposide as a preparative regimen. Blood 1993; 81:311-8.
40. Bloomfield CD, Lawrence D, Arthur DC, et al. Curative impact of intensification with high-dose cytarabine (HiDAC) in acute myeloid leukemia (AML) varies by cytogenetic group [abstract]. Blood 1994; 81(Suppl 1):111a. n. #431).
41. Bassan R, Battista R, Corneo G, et al. Idarubicin in the initial treatment of adults with acute lymphoblastic leukemia: the effect of drug schedule on outcome. Leuk Lymphoma 1993; 11:105-10.
42. Weiss M, Telford P, Kempin S, et al. Severe toxicity limits intensification of induction therapy for acute lymphoblastic leukemia. Leukemia 1993; 7:832-7.
43. List AF. The role of multidrug resistance and its pharmacological modulation in acute myeloid leukemia. Leukemia 1996; 10:937-42.
44. Preisler Hd, Raza A, Larson R, et al. Suppression of regrowth resistance and long remission durations in AML [abstract]. Blood 1996; 88(Suppl 1):218a. n. #861.
45. Perentesis JP, Kersey JH. Biologic therapy of leukemia. In: Henderson ES, Lister TA, Greaves MF. eds. Leukemia. Philadelphia: Saunders Co. 1996. p. 354-88.