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# Out-patient management of acute myeloid leukemia after consolidation chemotherapy. Role of a hematologic emergency unit

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Abstract

***Background and Objective.*** **Increasing attention to quality of life and to health care costs has recently induced several cancer centers to change in-patient management into an out-patient setting even during high risk phases of disease. The aim of this prospective study was to evaluate feasibility and safety, as well as clinical characteristics, of out-hospital management of AML patients during their post-consolidation phase.**

***Design and Methods.*** **All patients who were treated over a three year period by the three following protocols were included in the study: AML10 EORTC/GIMEMA for patients with AML, except for APL, aged ≤ 60 years; AML 13 EORTC/GIMEMA, for patients with AML, except for APL, aged >60 years; AIDA GIMEMA for APL patients. All patients submitted to the AML10 and AML13 protocols and those patients submitted to the AIDA protocol with difficult peripheral vein access had a central venous catheter (CVC) sited. Patients treated as in-patients were discharged at the end of consolidation chemotherapy provided they were in a good clinical condition. They were routinely evaluated on an out-patient basis twice weekly. In the event of any complication they were referred to the Emergency Unit of our Department dedicated to out-patients with hematologic diseases.**

***Results.*** **One hundred and eleven patients with AML were eligible for intensive chemotherapy. After achievement of complete remission they received a total of 133 consolidation courses and in 127 instances they were followed on an out-patient basis during the aplastic phase. There were 69 cases (54%) of rehospitalization, 68 because of fever and only one because of severe anemia. Rehospitalization occurred in 90%,70% and 38% of courses in AML10, AML13 and AIDA protocols, respectively. Only one patient died: the cuase of death was a brain hemorrhage. Coagulase negative staphylococci and viridans streptococci were the organisms most frequently isolated from blood. Most coagulase negative staphylococci were isolated in patients submitted to AML10 and AML13 protocols, who had an indwelling CVC. Empiric once-a-day antibacterial therapy with ceftriaxone and amikacin was effective in 75% of the cases and made early discharge possible in 28% of the cases with antibiotic therapy continued in an out-patient setting. Overall, patients were managed out of the hospital for 66% of the period of post-consolidation neutropenia (77%, 48% and 50% of the post-consolidation neutropenia period in patients treated with AIDA, AML10 and AML13 protocols, respectively).**

***Interpretation and Conclusions.*** **Thanks to the availability of an emergency unit specifically dedicated to out-patients with hematologic diseases, selected out-hospital management of AML patients during post-consolidation cytopenia is a feasible, well accepted and cost-saving option, and can contribute to lower the risk of developing severe nosocomial infections. The empiric therapy with once-a-day ceftriaxone plus amikacin was effective, with the exception of staphylococcal infections, and made it possible to discharge patients early to continue treatment in an out-patient setting.**


Key words: acute myeloid leukemia, out-patient, infections, emergency unit, ceftriaxone plus amikacin

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Disease-free survival (DFS) of patients with acute myeloid leukemia (AML) achieving complete remission (CR) after induction phase has been prolonged, in the recent years, by therapeutic approaches based on intensive consolidation treatments.[1,2] Improvement of DFS also requires accurate management of febrile and hemorrhagic episodes that frequently complicate the chemotherapy induced bone marrow (BM) aplasia implying prolonged patients' hospitalization.

Increasing attention to quality of life and to health care costs, in addition to the high risk of severe multiresistant nosocomial infections, has recently induced several cancer centers to change in-patient management into an out-patient setting even during high risk phases of disease.[3,4] However, the clinical implications of this policy have not yet been sys-

**Table 1. Chemotherapy protocols for AML patients.**

| | *AML-10 EORTC/GIMEMA* | *AML-13 EORTC/GIMEMA* | *AIDA GIMEMA* |
|---|---|---|---|
| ***Induction*** | IDA 10 mg/m² days 1-3 or<br>MITOX 12 mg/m² ,days 1-3 or<br>DNR 50 mg/m² , days 1-3<br>+ Ara-C 100 mg/m² c.i. ,days 1-10 | MITOX 7 mg/m², days 1,3,5<br>+ Ara-C 100 mg/m² c.i., days 1-7<br>+ VP-16 100 mg/m² c.i., days 1-3 | ATRA 45 mg/m²/day p.o.<br>+ IDA 12 mg/m², days 2, 4, 6, 8 |
| ***Consolidation*** | *Complete remission* | | |
| | **Arm IDIA:** IDA 10 mg/ m² i.v., days 4,5,6<br>Ara-C 500 mg/ m² i.v. bid,days 1-6<br>**Arm NOVIA:** MITOX 12 mg/ m² i.v.,days 4,5,6<br>Ara-C 500 mg/ m² i.v. bid,days 1-6<br>**Arm DIA:** DNR 50 mg/ m² i.v., days 4,5,6<br>Ara-C 500 mg/ m² i.v. bid ,days 1-6 | **Arm I.V. mini-ICE:** IDA 8 mg/m ² i.v., days 1, 3, 5<br>Ara-C 100 mg/m² c.i., days 1-5<br>VP-16 100 mg/m² i.v., days 1-3<br>**Arm oral mini-ICE:**# IDA 20 mg/m² orally, days 1, 3, 5<br>Ara-C 50 mg/m² s.c.bid, days 1-5<br>VP-16 100 mg/m² orally bid, days 1-3 | **Course 1:** Ara-C 1 g/m² x 6 h, days 1-4<br>IDA 5 mg/m², days 1-4<br>**Course 2:** MITOX 10 mg/m², days 1-5<br>VP-16 100 mg/m², days 1-5<br>**Course 3:**# IDA 12 mg/m² day 1<br>Ara-C 150 mg/m² s.c. tid, days 1-5<br>6-TG 70 mg/m² tid p.o., days 1-5 |

*IDA = idarubicin; MITOX= mitoxantrone; DNR= daunorubicin; Ara-C= cytosine arabinoside; VP-16= etoposide; 6-TG = 6-thioguanine . #Administered on an out-patient basis.*

tematically analyzed.

Such an approach is currently under investigation at our Institution in the emergency unit (EU), which is dedicated to out-patients with blood disorders requiring immediate clinical evaluation and therapeutic intervention for all kinds of hematologic emergencies.

In a preliminary study focused on patients with acute promyelocytic leukemia (APL), early discharge and ambulatory care of patients in post-consolidation phase proved to be a feasible option and allowed the patients to be safely managed out of the hospital during 80% of their period of cytopenia.[5]

The aim of this prospective study was to evaluate, over a three year period, feasibility and safety, as well as clinical characteristics, of out-hospital management of patients with all types of AML during the post-consolidation phase. The data were analyzed with respect to different chemotherapy protocols.

## Design and Methods

### *Patients*

All patients aged ≥ 20 years with a new diagnosis of AML who were treated at our hospital between July 1, 1996 and June 30, 1998 with intensive chemotherapy according to the following protocols were included in the study:

1. AML-10 EORTC/GIMEMA, for AML patients [with the exclusion of acute promyelocytic leukemia (APL)] aged ≤ 60-years.[6]
2. AML-13 EORTC/GIMEMA, for AML patients (with the exclusion of APL) aged ≥ 60 years.[7]
3. AIDA GIMEMA for patients affected by APL.[8] Some of these patients were included in the previous report focused on APL.[5]

Treatment schedules of the three protocols are summarized in Table 1.

### *Patients' management*

Patients were treated in ordinary wards during the induction phase until achievement of hematologic remission and normalization of peripheral blood counts. Post-remission consolidation chemotherapy was administered in an in-patient or out-patient setting according to the different protocols.

Usually, AML patients treated as in-patients were discharged at the end of the consolidation chemotherapy regardless of their absolute neutrophil or platelet count, providedthey were in a good clinical condition, without fever and/or bleeding and not receiving intravenous therapy.

Major complications occurring during the previous induction therapy were not considered a contraindication to early discharge after consolidation, as a criterion of eligibility for consolidation therapy was a their presumably complete regression. A condition for out-patient management in this post-consolidation phase was a relatively short distance between the patient's residence and the hospital (< 2 hr, by car). Patients living far from the hospital were allocated in a nearby residence for patients.

All patients submitted to the AML 10 and AML 13 protocols and those patients submitted to the AIDA protocol with difficult peripheral vein access had an indwelling central venous catheter (CVC) (Groshong catheter) sited. All patients received antibacterial and antihemorrhagic prophylaxis with oral ciprofloxacin (500 mg bid) and with oral tranexamic acid (100 mg/kg/day) plus prednisone (25 mg/day), which were administered until neutrophils rose to $1\times10^9$/L and platelets to $50\times10^9$/L, respectively.

Patients were routinely evaluated on an out-patient basis twice weekly; packed red blood cells and platelet concentrates were administered if hemoglobin concentration and platelet (PLTS) count were < 8 g/dL and < $10\times10^9$/L, respectively.

Patients were instructed to check their own vital parameters daily, including oral temperature, and to return immediately to our EU in case of fever (body temperature > 38°C) and/or other signs of infection, bleeding or any other complication. A 24 hour telephone line was also provided to the patients to communicate with the EU about any problem; a 6-bed ward especially designed for emergencies and short-term hospitalization was available in this unit.

Upon arrival at the EU, a complete clinical and laboratory check was performed. In the event of fever or other signs of infection, blood cultures were set up (at least three at intervals of 15 minutes) as well as cultures from any presumed site of infection, and a chest radiograph was performed. Patients with bleeding and febrile patients with profound thrombocytopenia ($<20\times10^9$/L) received platelet concentrates (1 unit/10 kg body weight/session).

Within 1 hour of arrival at the EU, patients with febrile neutropenia were admitted to the ward and empirically treated with a daily intravenous dose of ceftriaxone (2 g) plus amikacin (20 mg/kg). This therapy was adjusted when necessary according to response, results of cultures and sensitivity tests. Antibiotic treatment was continued until 4 consecutive days has passed without fever or until microbiological and/or clinical evidence of infection disappeared. Patients free from fever early and in a good clinical condition were usually discharged regardless of their absolute neutrophil count or platelet count and continued antibiotic therapy as out-patients. In the event of prolonged hospitalization, the patients admitted and initially treated at the EU ward were transferred to the ordinary wards of the hospital.

## Results

One hundred and eleven patients with AML were eligible for intensive chemotherapy during the study period. There were 53 males and 58 females. The mean age was 44 years (range, 20-72) The clinical data of these patients are described in Table 2. Thirty-four patients did not receive consolidation therapy because of early death (15 cases), resistance to induction therapy (13 cases) or clinical conditions contraindicating further intensive therapy (6 cases). Seventy-seven patients (35 males and 42 females) who achieved CR were consolidated with a total of 133 chemotherapy courses. Their mean age was 42 years (range, 20-69). In 127 instances, patients were discharged immediately after therapy administration or were treated as out-patients according to the protocol schedule, and then followed on an ambulatory basis during the phase of BM aplasia. Our analysis was concentrated on these cases. In 6 cases, early discharge was not possible due to development of an infective (5 cases) or other (one case) complication. Of these, one patient who had had a *P. aeruginosa* septicemia during the induction therapy developed a relapse of the infection during the hospitalization for consolidation treatment. A CVC was present in all patients submitted to the AML10 and AML13 protocols, and in only two patients with APL submitted to the AIDA protocol.

**Table 2. Patients grouped according to type and phase of cytotoxic therapy.**

| | *AIDA* | *AML13* | *AML10* | *Total* |
|---|---|---|---|---|
| Induction, no. of pts | 35 | 16 | 60 | 111 |
| Early death, no. of pts | 1 | 4 | 10 | 15 |
| Resistant, no. of pts | 0 | 3 | 10 | 13 |
| No. of pts not eligible for further chemotherapy | 0 | 0 | 6 | 6 |
| No. of pts consolidated after CR | 34 | 9 | 34 | 77 |
| No. of consolidation courses | 86 | 13 | 34 | 133 |
| No. of consolidation courses with early discharge (no.of pts) | 84 (32) | 12 (8) | 31 (31) | 127 (71) |

**Table 3. Characteristics of complications which required the patient to be rehospitalized in the EU.**

| *Courses* | *AIDA (84)* | *AML13 (12)* | *AML10 (31)* | *Total (127)** |
|---|---|---|---|---|
| | | *No. of cases* | | |
| No. of rehospitalizations (%)° | 32 (38) | 9 (78) | 28 (90) | 69 (54) |
| Fever of unknown origin | 17[#] | 2 | 8 | 27 |
| Microbiologically documented infections | 12 | 7 | 16 | 35 |
| Clinically documented infections | 2 | 0 | 4 | 6[§] |
| Severe anemia | 1 | 0 | 0 | 1 |

**In 71 patients; °in 52 patients (AIDA, 18 pts; AML13, 6 pts; AML10, 28 pts). [#]One patient died due to brain hemorrhage; [§]pneumonia (three cases), probable hepatosplenic candidiasis (one case) and perirectal abscess (two cases).*

Throughout the period from discharge to recovery from BM aplasia the patients were seen a mean of 2 times (range 0-4) and received a mean of 2 packed red blood cells (range, 0-4) and 1.5 platelet concentrate transfusions (range 0-3) in a day-hospital regimen.

As detailed in Table 3, after the 127 consolidation courses followed by ambulatory management, there were 69 cases (54%) of rehospitalization for fever (68 cases) or severe anemia (one case)

Rehospitalization occurred in 90%, 78% and 38% of courses of the AML10, AML-13, and AIDA protocols, respectively. There was no significant correlation between age and the need for re-hospitalization (Wilcoxon Rank Sum Test, $p > 0.05$). On patient admission, mean neutrophil count was 40/mm$^3$ (range 0-200/mm$^3$), mean platelet count was 9,000/mm$^3$ (range 4,000-30,000), and mean hemoglobin level was 8.6 g/dL (range 5.5-10.5). On admission to the EU, in 63 instances the patients were in a good clinical con-

**Table 4. Microbiologically documented infections in out-patients submitted to consolidation chemotherapy for AML. Microbial isolates and site of infection.**

| *Isolates (number of cases)* | *Septicemia** | *Other sites* | *AIDA* | *AML 13* | *AML 10* |
|---|---|---|---|---|---|
| | | *No. of cases* | | | |
| Gram-negative (10) | | | | | |
| *P. aeruginosa* (2) | 1 | 1° (cellulitis) | 1 | 0 | 1 |
| *E. coli* (5) | 5 | - | 1 | 1 | 3 |
| *Enterobacter cloacae* (2) | 2 | - | 1 | 0 | 1 |
| *Fusobacterium* (1) | 1 | - | 1 | 0 | 0 |
| Gram-positive (23) | | | | | |
| Coagulase$^{neg}$ *Staphylococcus* (14) | 14 | - | 2 | 5 | 7 |
| *Streptococcus viridans* (9) | 5 | 3° (interstitial pneumonia) | 5 | 1 | 3 |
| Polymicrobial (*E.coli*+*S.aureus* ) (1) | 1 | - | 0 | 0 | 1 |
| *Aspergillus fumigatus* (1) | | 1 (pulmonary mycetoma) | 0 | 0 | 1 |

**Without signs of organ involvement; °with septicemia.*

**Table 5. Out-patient and in-hospital management of 127 post-remission consolidation courses for AML.**

| *Courses* | *AIDA (84)* | *AML13 (12)* | *AML10 (31)* | *Total (127)* |
|---|---|---|---|---|
| ***Hospitalization for chemotherapy administration*** | | | | |
| Mean days | 4.1 | 3.2 | 6.9 | 4.7 |
| (range) | (0-7) | (0-11) | (6-8) | (0-11) |
| ***Rehospitalization°*** | | | | |
| Mean days | 11.1 | 14.3 | 12.1 | 11.9° |
| (range) | (3-70) | (7-37) | (1-26) | (1-70) |
| ***Post-consolidation neutropenia**** | | | | |
| Mean days | 18.1 | 20.7 | 21.1 | 19.1 |
| (range) | (14-77) | (16-50) | (16-35) | (14-77) |
| ***Out-patient neutropenia*** | | | | |
| Mean days | 13.9 | 10.5 | 10.2 | 12.7 |
| (%) | (77%) | (50%) | (48%) | (66%) |
| (range) | (5-27) | (5-20) | (3-20) | (3-27) |

*°After 69 courses. *Time of neutrophil count < 500/mm$^3$.*

dition. Five patients with septic shock and one patient with a symptomatic anemia (Hb 5.5 g/dL) rapidly recovered with treatment. One APL patient readmitted to the EU because of fever after the Ist consolidation course of the AIDA protocol developed a fatal brain hemorrhage 1 h after hospitalization.

Febrile episodes were of unknown origin in 27 cases (39.7%); an infection was clinically documented in 6 cases (8.7%) and microbiologically documented in 35 cases (50.7%), 34 of which were septicemias (Table 4).

Coagulase negative staphylococci and viridans streptococci were isolated in 14 and 9 cases, respectively. Most of coagulase negative staphylococci were isolated in patients submitted to AML 13 (5 cases) and AML 10 (7 cases) protocols and in only two patients with APL. In the five patients presenting in septic shock, septicemias due to *E.coli* (2 cases), *E.coli* plus *S.aureus* (one case), *P.aeruginosa* (one case) and *Streptococcus viridans* (one case) were documented. All Gram-negative isolates but one *P.aeruginosa* and one *Enterobacter cloacae* were susceptible *in vitro* to ceftriaxone and amikacin. Streptococci were susceptible to both ceftriaxone and amikacin in 100% of the cases, whereas staphylococci were susceptible to the two single drugs in 33% and 66% of the cases, respectively (53% of staphylococci were susceptible to oxacillin and 100% to vancomycin and teicoplanin). The two patients with septicemia due to *P. aeruginosa* and *Enterobacter cloacae* resistant to ceftriaxone and amikacin had developed an infection with the same microorganisms during the previous induction treatment.

Fifty out of 67 (75%) treated febrile episodes responded to the initial empiric therapy with ceftriaxone plus amikacin while in 17 cases the fever disappeared after treatment modification (addition of teicoplanin in 11 cases, substitution of ceftriaxone with meropenem in 2 cases, addition of teicoplanin followed by amphotericin B in 4 cases). The initial empiric antibiotic therapy was effective in 26/30 (87%), 5/9 (56%) and 19/28 (68%) patients submitted to AIDA, AML13 and AML10 protocols, respectively.

The mean time to readmission to the EU was 9.2 days (range 3-15) from the end of chemotherapy. As detailed in Table 5, patients rehospitalization lasted a mean of 11.9 days (range 1-70). Nineteen of 67 (28.4%) patients treated for infective complications were discharged early after a mean of 3.8 days (range 1-6), regardless of their neutrophil and platelet count, to continue once-a-day antibiotic therapy with ceftriaxone plus amikacin as out-patients for a further mean 4.3 days (range 3-6). The other 48 patients received the complete antimicrobial therapy as in-patients.

Overall, eighteen of 69 (26%) patients admitted to the EU ward were eventually transferred to the ordinary ward of our hospital for a cumulative total of 155 days, which represented 18.8% of the total number of days of rehospitalization.

The cumulative duration of post-consolidation neutropenia was 2,423 days (mean 18.9 days per patients; range 14-77). Our policy allowed the patients in this treatment phase to be managed out of the hospital for a cumulative total 1,607 days (a mean of 12.5 days per patient), which represents 66% of the post-consolidation neutropenia period. In particular, we estimate that patients treated with AIDA, AML10 and AML13 protocols were managed as out-patients in 77%, 48% and 50% of the post-consolidation neutropenia period, respectively. There was no significant correlation between age and days spent as an out-patient (Spearman's test, $p$=0.09).

## Discussion

Out-patient management of leukemia patients is becoming an increasingly used practice in several cancer centers even during phases of neutropenia and thrombocytopenia.[9-11] The risks and benefits of such a policy have not, however, yet been systematically investigated and, to our knowledge, only preliminary experiences have so far been published.[3,4] In a prospective observational analysis Gillis *et al*.[3] evaluated 29 AML patients who received a total of 86 chemotherapy courses. Out of 50 patients discharged early, mostly after consolidation treatments, 47 (94%) were readmitted to hospital and only two deaths occurred. The authors concluded that selected discharge of patients during chemotherapy-induced neutropenia was generally safe and led a 16% saving of hospitalization.

At our center, a preliminary analysis of this policy focused on APL patients submitted to consolidation cycles of the AIDA protocol.[5] Out-patient management proved to be the option of choice, as rehospitalization was required for only 24% of the neutropenia period.

The evaluation extended to patients with all subtypes of AML appears to confirm that early discharge coupled with out-patient care can represent a feasible option in patients submitted to post-remission consolidation therapy. Complications occurred during previous induction therapy did not influence the policy of early discharge in patients eligible for consolidation therapy as only one of our patients developed an infection relapse before discharge.

Overall, only 54% of the cases required rehospitalization, while the remaining 46% were managed on an out-patient basis throughout the whole period of induced aplasia. Differently from APL patients who were rehospitalized in only 38% of the cases, the majority of patients with other AML subtypes required rehospitalization (90% and 78% of patients submitted to AML 10 and AML 13 protocols, respectively). Nevertheless, at least 50% of the post-consolidation neutropenia period was managed out of the hospital also in this group of patients.

Rehospitalization did not appear to be more frequent in older patients and age did not influence the rate of out-patient neutropenia. Thanks to the availability of a brief stay ward in the EU, only 18.8% of the rehospitalization time was spent in the ordinary wards of our hematologic center.

In all but one instance, rehospitalization was due to development of fever during severe neutropenia. In most of the cases patients were and continued to be in a good general condition; even the five patients who presented to the EU in septic shock rapidly improved without sequelae. Only one patient, a 61-year old woman with APL, died soon after readmission of a brain hemorrhage while she was febrile and severely thrombocytopenic.

In one half of the febrile episodes the infection was microbiologically documented. Coagulase negative staphylococci were the most common causes of bacteremia accounting for 40% of the bloodstream isolates and were mainly detected in patients with AML other than APL. This was an expected occurrence considering that most of the patients submitted to the AML10 and AML13 protocols had an indwelling CVC, differently from patients submitted to the AIDA protocol. In agreement with previous reports,[3] there was a low incidence of multiresistant micro-organisms. We do not have data on the incidence of multiresistant nosocomial pathogens in a control population in our Center. On the other hand, only two patients of the present series developed a septicemia due to resistant *P.aeruginosa* and *E. cloacae*, and in both cases the same micro-organisms had been previously isolated while the patients were hospitalized for remission induction treatment. These data seem to confirm the suggestion that out-hospital management of neutropenic patients is associated with a lower incidence of infections caused by resistant pathogens; nevertheless, the possibility of their relationship with a previous hospitalization must be considered.

The association of ceftriaxone plus amikacin has been shown to be effective and suitable for empiric treatment of hospital-acquired infections in neutropenic cancer patients.[12-14] At our Institution,[11,14,15] this antibiotic regimen has been widely used in the last decade as empiric treatment of febrile neutropenia also because the once-a-day intravenous administration is easy use and has economic advantages[13,16] particularly in the setting of out-hospital management.

In the present study, this empiric treatment proved to be effective in 75% of the febrile episodes and allowed the early discharge of 28% of patients who continued once-a-day antibiotic therapy as out-patients. Staphylococcal infection related to the presence of a CVC was the main cause of failure of the initial empiric therapy. The addition of a glycopeptide (teicoplanin) was required in the cases unresponsive to this approach. The low incidence of staphylococcal infections in patients submitted to the AIDA protocol, which usually does not require a CVC, seems to explain the particularly high efficacy of the ceftriaxone and amikacin association (87% of responses) in APL patients.

We conclude that selected out-hospital management during post consolidation cytopenia is a feasible, well-accepted and cost-saving option in all patients with AML, as most of the neutropenia period can be managed out of hospital. This policy seems to be reasonable in older as well as younger patients. An adequate *education* of the patients appears to be of crucial importance in the feasibility of the out-patient program.

This practice contributed to sparing these immunocompromized subjects the risk of developing infections caused by highly pathogenic and antimicrobial resistant nosocomial isolates.

The empiric therapy of febrile patients with once-a-day ceftriaxone plus amikacin was effective, with exception for staphylococcal infections, and made possible early discharge and continuation of the antibiotic therapy in an out-patient setting.

The EU specifically dedicated to out-patients with hematologic diseases proved to be of crucial importance in the early management of complications; the presence of a ward for short term hospitalizations proved to be relevant in the policy of hospital bed saving and of a quick patient turnover in the whole hematologic center.

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*CG, GA and FM formulated the design of the study and wrote the paper. CG, GA, RL, LC, AS, SM, AT, GC were responsible for the clinical assessment and data handling. ST, GD, SGM and FC collected the clinical data.*

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### Disclosures

*Conflict of interest: none.*

*Redundant publications: previous experience accepted for publication in Leukemia cited in the discussion of the present paper.*

### Manuscript processing

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