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### Authors
Daver, Naval
Kantarjian, Hagop
Marcucci, Guido
et al.



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# Clinical Characteristics and Outcomes in Patients with Acute Promyelocytic Leukaemia and Hyperleucocytosis

**Naval Daver**[1], **Hagop Kantarjian**[1], **Guido Marcucci**[2], **Sherry Pierce**[1], **Mark Brandt**[1], **Courtney Dinardo**[1], **Naveen Pemmaraju**[1], **Guillermo Garcia-Manero**[1], **Susan O'Brien**[1], **Alessandra Ferrajoli**[1], **Srdan Verstovsek**[1], **Uday Popat**[3], **Chitra Hosing**[3], **Paolo Anderlini**[3], **Gautam Borthakur**[1], **Tapan Kadia**[1], **Jorge Cortes**[1], and **Farhad Ravandi**[1]

[1]Departments of Leukemia, The University of Texas M.D. Anderson Cancer Center, Houston, Texas

[2]Department of Internal Medicine, The Ohio State University, Columbus, Ohio

[3]Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas M.D. Anderson Cancer Center, Houston, Texas

## Summary

The clinical characteristics, treatment options and outcomes in patients with acute promyelocytic leukaemia (APL) and hyperleucocytosis remain poorly defined. This study reviewed 242 consecutive patients with APL; 29 patients (12%) had a white blood cell count (WBC) ≥ 50 × $10^9$/l at presentation (median WBC 85.5 × $10^9$/l). Patients with hyperleucocytosis had inferior complete remission (CR) rates (69% versus 88%; *P*=0.004) and higher 4-week mortality (24% versus 9%; *P*=0.018) compared to patients without hyperleucocytosis. We noted a trend towards inferior 3-year disease-free survival (DFS) (69% versus 80%; *P*=0.057) and inferior 3-year overall survival (OS) (74% versus 92%; *P*=0.2) for patients with hyperleucocytosis. Leukapheresis was performed in 11 (38%) of the 29 patients with hyperleucocytosis. CR rate and 3-year OS were not significantly improved in patients who received leukapheresis. CR rate and 3-year OS for the 15 patients with hyperleucocytosis treated with all-trans retinoic acid (ATRA) plus arsenic trioxide (ATO) plus cytotoxic therapy (idarubicin or gemtuzumab ozogamicin) combinations were 100% and 100% versus 57% and 35% for the 14 patients treated with non-ATRA/ATO combinations (*P*=0.004 and *P*=0.002). Leukapheresis does not improve the outcomes in patients with APL presenting with hyperleucocytosis. ATRA/ATO-based combinations are superior to other regimens in these patients.

Correspondence: Farhad Ravandi, Department of Leukemia, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Unit 0428, Houston, TX 77030, Phone: 713-745-0394, fravandi@mdanderson.org.

**Author contributions**: ND and FR wrote the paper; FR, ND, GM, and HK designed and coordinated the study; FR, HK, CD, NP, GM, SO, AF, SV, UP, CH, PA, GB, TK, JC enrolled the patients and conducted the research; SP, MB, FR and ND analysed the data and performed the statistics. All of the authors participated in the discussion and have reviewed and approved the current version of the manuscript.

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**Keywords**

acute promyelocytic leukaemia; outcomes; leukapheresis; arsenic; ATRA

## Introduction

The differentiating agent all-trans retinoic acid (ATRA) has revolutionized the therapy of acute promyelocytic leukaemia (APL)(Huang, *et al* 1988, Tallman, *et al* 1997, Warrell, *et al* 1991). Induction therapy with ATRA in combination with chemotherapy resulted in complete remission (CR) rates greater than 90% with improved disease-free survival (DFS) and overall survival (OS)(Burnett, *et al* 1999, Fenaux, *et al* 1999). Arsenic trioxide (ATO) induces apoptosis and differentiation of leukaemic promyelocytes and is highly active in patients with relapsed APL (Chen, *et al* 1997, Shen, *et al* 1997, Soignet, *et al* 2001). The combination of ATRA and ATO has been safe and effective in the frontline setting and, at least in the patients with low and intermediate risk disease, superior to ATRA plus anthracycline (Jing, *et al* 2001, Lo-Coco, *et al* 2013, Ravandi, *et al* 2009, Shen, *et al* 2004).

Acute myeloid leukaemia (AML) patients presenting with an elevated white blood cell count (WBC) at diagnosis have a poor prognosis (Burnett, *et al* 1999, Estey, *et al* 1982, Giles, *et al* 2001, Glidewell and Holland 1975, Ventura, *et al* 1988). Several studies have demonstrated the clinical significance of a high presentation WBC in patients with APL, with a WBC $\geq 10 \times 10^9$/l considered high risk for relapse and adverse outcome (Burnett, *et al* 1999, Lo-Coco, *et al* 2013, Sanz, *et al* 2000). Burnett et al (1999) noted that the only factor that influenced treatment outcome among patients with APL treated with daily ATRA in combination with chemotherapy was the WBC at presentation, wherein patients with WBC $>10 \times 10^9$/l had an inferior CR rate, DFS and OS with a higher incidence of relapse and early mortality. Fenaux et al (1999) noted that even a modest increase in WBC adversely impacted the outcome of patients treated with ATRA in combination with chemotherapy, with a significantly inferior event-free survival (EFS) in patients with WBC $> 5 \times 10^9$/l as compared to patients with WBC $\leq 5 \times 10^9$/l at diagnosis. Similarly, inferior results have been reported in patients with elevated WBC after treatment with ATO-based frontline regimens (Alimoghaddam, *et al* 2011, Estey, *et al* 2006, Mathews, *et al* 2006, Ravandi, *et al* 2009). It has been postulated that leucocytosis at presentation or during the course of therapy with ATRA and/or ATO may be associated with a higher incidence of differentiation syndrome (Fenaux, *et al* 1992, Fenaux, *et al* 1993). However, Vahdat et al (1994) noted that neither the initial leucocyte count nor the rate of rise in leucocytes were sufficiently accurate clinical predictors for developing differentiation syndrome.

Several prior studies have evaluated the role of leukapheresis in patients with AML and hyperleucocytosis (Bug, *et al* 2007, De Santis, *et al* 2011, Fenaux, *et al* 1999, Giles, *et al* 2001, Thiebaut, *et al* 2000). Giles et al evaluated the role of therapeutic leukapheresis in patients with AML (excluding APL) and WBC $\geq 50 \times 10^9$/l at presentation (Giles, *et al* 2001). Patients who underwent leukapheresis had a reduced two-week mortality ($P$ = 0.0056) and a trend towards higher CR rates ($P$=0.059). Ironically, there was a trend towards inferior OS for patients who underwent leukapheresis ($P$=0.06). In patients with APL, it was

noted that neither leukapheresis nor low-dose chemotherapy reduced the frequency or severity of differentiation syndrome in patients who developed leucocytosis during treatment with ATRA (Vahdat, *et al* 1994). However, the role of early leukapheresis in patients with APL who present with hyperleucocytosis at diagnosis remains poorly defined. We conducted this retrospective review at The University of Texas M.D. Anderson Cancer Center (MDACC) to assess the impact of therapeutic leukapheresis in patients with newly diagnosed APL who have a WBC $\geq 50 \times 10^9$/l at presentation.

## Materials and methods

### Patients

We retrospectively reviewed the records of patients with APL treated at our institution between January 1990 and December 2011. This study was approved by the Institutional Review Board. We stratified the patients into 3 groups: WBC $< 10 \times 10^9$/l, WBC 10 - 49.9 $\times 10^9$/l, and WBC $\geq 50.0 \times 10^9$/l. OS and DFS were qualitatively different in the three groups, with patients who had a WBC $> 50.0 \times 10^9$/l on presentation having inferior outcomes (Figure 1A and 1B). Hence, a WBC of $\geq 50 \times 10^9$/l was chosen for further analysis.

### Statistical Methods and Definitions

We examined the baseline clinical and biological characteristics, date of initial therapy, treatment modality, date and number of cycles of leukapheresis, response to treatment, 4-week mortality, DFS, OS and 3-year OS. CR was defined as presence of fewer than 5% blasts and promyelocytes with normal haematopoiesis in the bone marrow as well as neutrophil count $> 1 \times 10^9$/l and platelet count $> 100 \times 10^9$/l in the peripheral blood. DFS was measured from the date of CR until relapse. OS was defined as the time from presentation to death from any cause or the last follow-up.

Differences among variables were evaluated by the chi-square test and Mann-Whitney *U* tests for categorical and continuous variables, respectively. All *P* values were two-sided and $P<0.05$ was significant. Survival distributions were estimated using the Kaplan–Meier method and the differences were compared using the log-rank test. Univariate and multivariate analyses were performed to identify potential prognostic factors associated with CR rate and OS. These factors included age, gender, cytogenetics, presence of clinical stasis, WBC, platelet count, fibrinogen level, leukapheresis and induction regimen. Statistical analyses were carried out using IBM SPSS Statistics 21 for Windows (SPSS Inc., Chicago, Illinois).

## Results

### Patient Characteristics

Two hundred and forty-two patients with APL were treated at MDACC between January 1990 and December 2011. Twenty-nine patients (12%) had a WBC $\geq 50 \times 10^9$/l at presentation (arbitrarily defined as the hyperleucocytosis group) and 213 patients (88%) had a WBC $< 50 \times 10^9$/l (non-hyperleucocytosis group).

### Characteristics of patients with hyperleucocytosis (WBC ≥ 50 × $10^9$/l)

Median WBC, peripheral promyelocyte percentage, haemoglobin and platelet count for the patients with hyperleucocytosis at diagnosis were 85.5 × $10^9$/l (range, 53.8-194.8), 86.5% (range, 0-97), 96 g/l (range, 7.7-12.8), and 25 × $10^9$/l (range, 10-124), respectively. Karyotype analysis was available in 28 (97%) patients with hyperleucocytosis. Twenty-five patients harboured the t(15:17)(q22; q21). Three patients did not manifest t(15:17) at presentation but had morphology consistent with APL and a detectable *PML-RARA* transcript. Additional cytogenetic abnormalities involved chromosome 9 in 3 (10%), chromosome 21 in 2 (7%), and chromosome 22, 6, 8, 12, hypodiploidy and hyperdiploidy in 1 (3%) each. Thirteen (45%) patients had the microgranular variant of APL. *PML-RARA* transcripts were detectable in all patients with a median transcript value of 24.0 (range, 0.13 - 42.7). *FLT3* mutation analysis was performed in 9 patients presenting after 2003 (the start of routine *FLT3* mutation testing at our institution) with all 9 (100%) having *FLT3*-internal tandem duplication (ITD) mutation and one having both *FLT3*-ITD and *FLT3*-tyrosine kinase domain (TKD) D835 mutations. No *RAS* or *KIT* mutations were identified. 23 (79%) patients had clinical evidence of leucostasis at presentation including hypoxia in 10 (34%), haemoptysis or diffuse alveolar haemorrhage in 6 (21%), stroke or intracranial bleeding in 4 (14%), intraocular bleeding in 4 (14%) and gastrointestinal bleeding in 4 (14%). Chemical disseminated intravascular coagulation was identified in 27 (93%) patients, with a median fibrinogen of 2.5 mg/l (range, 65 - 700), median prothrombin time of 16.6 s (range, 12.6 - 24.2) and median partial thromboplastin time of 25 s (20.8 - 36.7).

### Characteristics compared to patients without hyperleucocytosis

Demographic and disease characteristics were compared between the 29 patients with WBC ≥ 50 × $10^9$/l and the 213 patients with WBC < 50 × $10^9$/l at presentation (Table I). The two groups were well matched for age, gender, presence of antecedent haematological disorder, exposure to prior chemotherapy or radiation therapy, cytogenetics, presenting fibrinogen and haemoglobin. Patients with hyperleucocytosis more frequently harboured the short-form *PML-RARA* transcript ($P$=0.001) and *FLT3*-ITD mutations ($P$<0.001) and had a higher bone marrow blast+promyelocyte percentage ($P$<0.001), lower platelet count ($P$=0.04), higher prothrombin time ($P$<0.001) and lower partial thromboplastin time ($P$=0.03) at presentation.

### Outcomes and survival for patients with hyperleucocytosis (WBC ≥ 50 × $10^9$/l)

Leukapheresis was performed in 11 (38%) patients with hyperleucocytosis with a median of 3 leukapheresis procedures (range, 1 - 6). Median WBC at initiation and completion of leukapheresis were 106.0 × $10^9$/l (range, 80.2 - 194.8 × $10^9$/l) and 26.1 × $10^9$/l (range, 1.7 - 35.9 × $10^9$/l), respectively. The decision to undergo leukapheresis was at the discretion of the treating physician. There were no laboratory or disseminated intravascular coagulopathy triggers that prompted the initiation of leukapheresis. The value of leukapheresis in AML patients in general and APL patients remains poorly defined, with no specific guidelines supporting or rejecting the use of leukapheresis in APL patients. Treatment regimens included ATRA plus ATO combinations in 15 (52%) patients including ATRA plus ATO plus idarubicin (IDA) in 4 (14%) and ATRA plus ATO plus gemtuzumab ozogamicin (GO) in 11 (38%). Of note, all patients treated with ATRA and ATO received early cytoreductive

therapy with either IDA or GO. Among the 4 patients who received IDA with ATRA and ATO, three patients received 3 consecutive days of IDA at a dose of 12 mg/m$^2$/day and one patient received 2 consecutive days of IDA at a dose of 12 mg/m$^2$/day. All 11 patients who received GO with ATRA and ATO received one dose of GO 9 mg/m$^2$/day on day 1 of the treatment. Non-ATRA/ATO regimens were used in 14 (48%) patients including ATRA plus IDA in 8 (27%), ATRA plus GO in 4 (14%) and ATRA plus IDA plus GO in 2 (7%), respectively. 7 patients died within 4 weeks of initiating therapy. Of the remaining 22 patients, 20 had morphological CR after induction with median time to CR of 21.5 days (range, 15 - 35), 1 patient had no response to induction and another died beyond 4 weeks. 6 patients relapsed and 5 achieved a second CR with salvage regimens including allogeneic stem cell transplant in 2 patients.

Univariate analysis of the potential prognostic factors associated with CR rate and OS in this patient population is shown in Table II. CR rate and 3-year OS for the 11 patients who received leukapheresis were 82% and 73% versus 78% and 67% for the 18 patients who did not receive leukapheresis ($P$=0.79 and $P$=0.64; respectively) (Fig 2A). CR rate and 3-year OS for the 15 patients treated with ATRA/ATO-based combinations were 100% and 100% versus 57% and 35% for the 14 patients treated with non-ATRA/ATO combinations ($P$=0.004 and $P$=0.002, respectively) (Fig 2B). Furthermore, we analysed outcomes based on the duration of ATRA therapy. A total of 16 patients received <6 months of ATRA therapy, including 9 patients on IDA+ATRA protocol and 7 patients on ATO+ATRA +IDA/GO. A total of 13 patients received >6 months of ATRA, including 3 patients on the GO+ATRA protocol and 10 patients on the ATO+ATRA+GO protocol. We did not identify a meaningful difference in OS and DFS among patients who received <6 months of ATRA therapy and those that received >6 months of ATRA therapy (Figure 3A and 3B).

### Outcomes compared to patients without hyperleucocytosis

APL patients with hyperleucocytosis had significantly lower CR rates (69% versus 88%; $P$=0.004) and higher 4-week mortality (24% versus 9%; $P$=0.018) as compared to those without hyperleucocytosis (Table III). The median OS and median DFS have not been reached in either group. (Fig 2A and 2B). However, there was a trend towards inferior 3-year DFS (69% versus 80%; $P$=0.057) and inferior 3-year OS (74% versus 92%; $P$=0.2) in the hyperleucocytosis group.

## Discussion

Hyperleucocytosis in the setting of acute leukaemia is generally defined by the presence of a WBC $\geq 50 \times 10^9$/l and is associated with a higher incidence of early mortality and a worse OS. Management depends upon the rapid reduction of patient's peripheral white cell count. Rapid cytoreduction may be achieved through either leukapheresis or cytoreductive chemotherapy.

The outcomes among patients with AML and hyperleucocytosis at presentation are generally poor (Table IV)(Burnett, *et al* 1999, Estey, *et al* 1982, Giles, *et al* 2001, Glidewell and Holland 1975, Ventura, *et al* 1988). A number of studies have evaluated the role of early leukapheresis in patients with hyperleucocytosis at presentation. Despite conflicting results

from various studies including the aforementioned studies, leukapheresis continues to be used in the setting of leucostasis as a life-saving procedure and for rapid reversal of leucostasis-related symptoms (Zuckerman, *et al* 2012).

The outcomes of APL patients with hyperleucocytosis and the role of leukapheresis in this setting have hitherto not been extensively evaluated. In the current report, patients with APL and hyperleucocytosis (WBC ≥ $50 \times 10^9$/l) at presentation had a significantly decreased CR rates and an increased early mortality as compared to patients without hyperleucocytosis. The median OS and DFS have not been reached for both groups. However, there is a trend towards inferior 3-year DFS and OS among the patients with hyperleucocytosis. Leukapheresis was performed in 11 (38%) patients with a median of 3 leukapheresis cycles and the procedure was an efficient means of cytoreduction. In spite of rapid cytoreduction the median OS and 3-year OS were not significantly improved. In general it is recommended that central venous catheterization and invasive procedures should be avoided in patients with APL during remission induction due to the high risk of haemorrhagic complications. APL patients who have hyperleucocytosis have an even higher risk of haemorrhage. Insertion of a large-bore venous catheter and leukapheresis may further exacerbate the coagulopathy. Vahdat et al (1994) noted a high risk of induction death among patients with who underwent leukapheresis. An expert panel on behalf of the European LeukaemiaNet did not recommend leukapheresis for APL patients presenting with leucocytosis and encouraged the initiation of chemotherapy and steroids on day 1 (within a few hours of the first dose of ATRA) to control the coagulopathy and reduce the risk of differentiation syndrome in these patients (Sanz, *et al* 2009). Similarly, our experience does not support routine leukapheresis for patients with APL who present with leucocytosis. However, the procedure may still have a therapeutic role in patients presenting with severe leucocytosis or end organ damage from leucostasis. The decision to initiate leukapheresis should be made on a case-by-case-basis after duly considering all the risks and benefits of this procedure in the individual patient.

Lo-Coco et al (2013) have shown the efficacy and safety of ATRA in combination with ATO in patients with low-to-intermediate risk APL. Here we demonstrate that, on multivariate analysis, among patients with very high risk APL, the only factor that significantly impacted the CR rate and 3-year OS was the choice of regimen. Fifteen patients who received frontline therapy that included both ATRA and ATO achieved a CR rate of 100% with 100% of the patients alive at 3 years. Of note, all the APL patients with hyperleucocytosis who were treated with frontline ATRA and ATO underwent early cytoreduction with either IDA 12 mg/m$^2$/day for 2-3 days (4 patients) or one dose of GO 9 mg/m$^2$/day (11 patients). In all cases, the IDA or GO was initiated on day 1 within a few hours of the first dose of ATRA. The early leucoreduction afforded by these cytotoxic agents allowed successful continuation of ATRA and ATO with excellent results. In contrast, the 14 patients who received frontline combinations that did not include both ATRA and ATO had a significantly inferior CR rate (CR rate = 57%). These patients also underwent early leucoreduction with IDA (8 patients), GO (4 patients) or both agents (2 patients). In spite of this, they had a significantly inferior 3-year OS of 35%. The duration of ATRA therapy did not impact the outcomes as there were no meaningful difference in OS and DFS among patients who received <6 months of ATRA therapy and those that received

>6 months of ATRA therapy. These findings indicate that frontline therapy that includes both ATRA and ATO is safe and preferable in high-risk patients with APL (WBC ≥ 50 × $10^9$/l). Furthermore, the development of a highly effective frontline regimen seems to obviate the inferior prognosis historically associated with traditional high-risk features.

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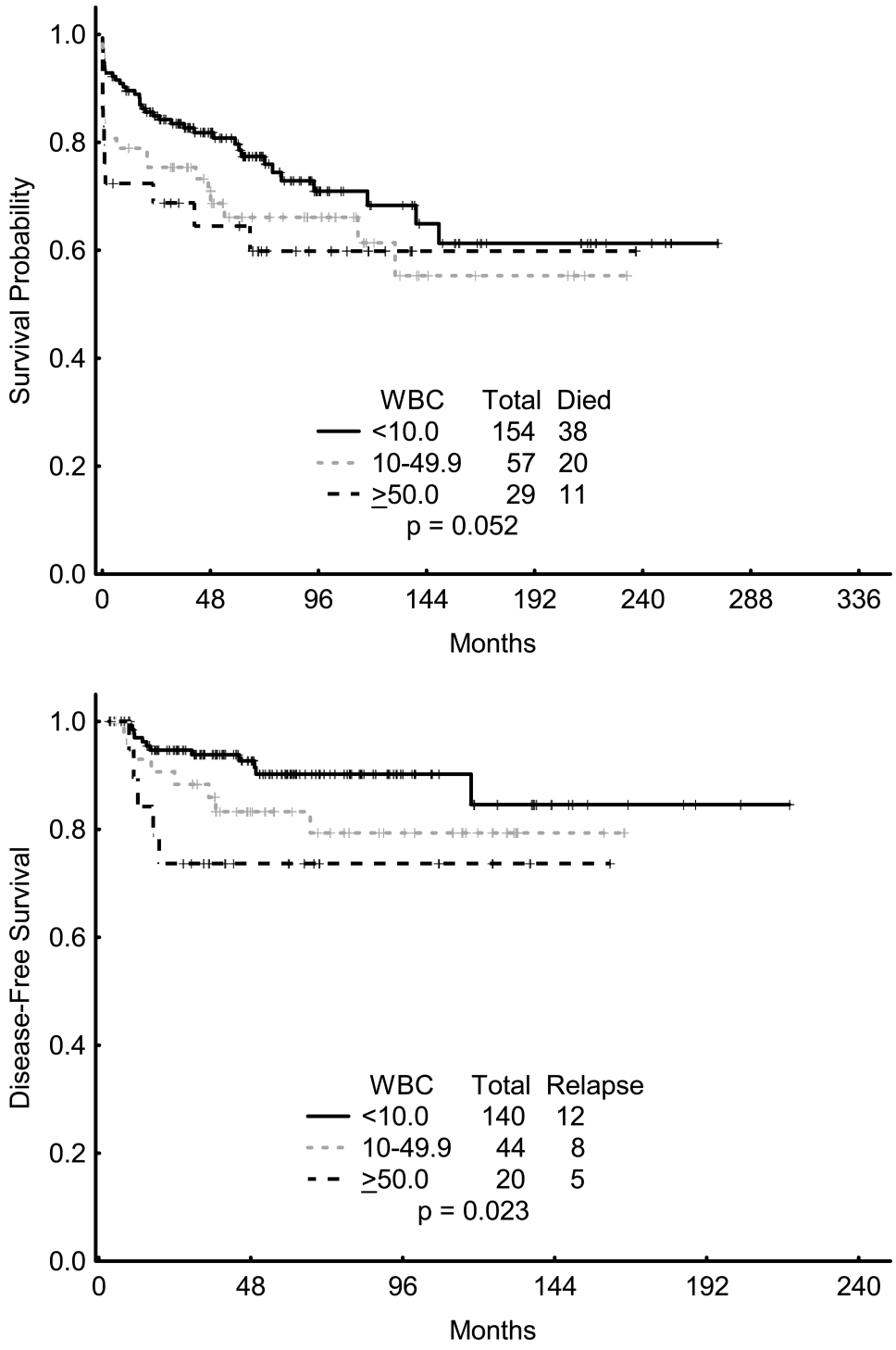


**Fig 1.**

Overall survival (A) and disease-free survival (B) among APL patients with WBC < 10 × $10^9$/l, WBC 10 - 49.9 × $10^9$/l, and WBC ≥ 50.0 × $10^9$/l. The curves demonstrate that OS and DFS are qualitatively different in the three groups, with patients who had a WBC ≥ 50.0 ×

$10^9$/l on presentation having inferior outcomes. APL, acute promyelocytic leukaemia; WBC, white blood cell count; OS, overall survival; DFS, disease-free survival.

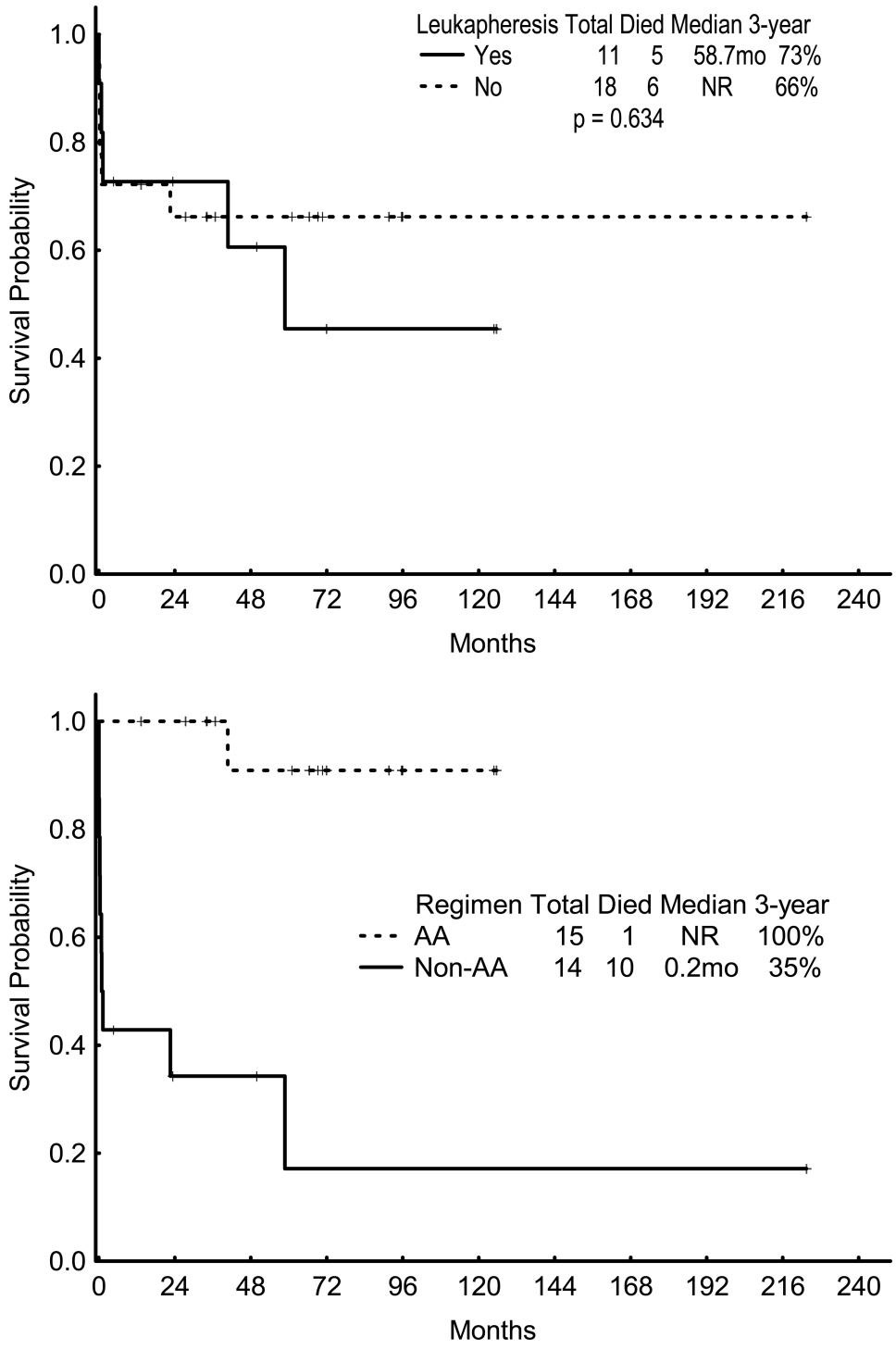


**Fig 2.**

Survival in APL patients with hyperleucocytosis (A) Overall survival leukapheresis versus no leukapheresis for patients with newly diagnosed APL who have a WBC ≥ 50 × $10^9$/l at presentation (B) Overall survival ATRA/ATO regimen (AA) versus Other regimens (ATRA/chemo, non-AA) for patients with newly diagnosed APL who have a WBC ≥ 50 ×

$10^9$/l at presentation. APL, acute promyelocytic leukaemia; WBC, white blood cell count; ATRA, all-trans retinoic acid; ATO, arsenic trioxide; NR, no response; mo, months.

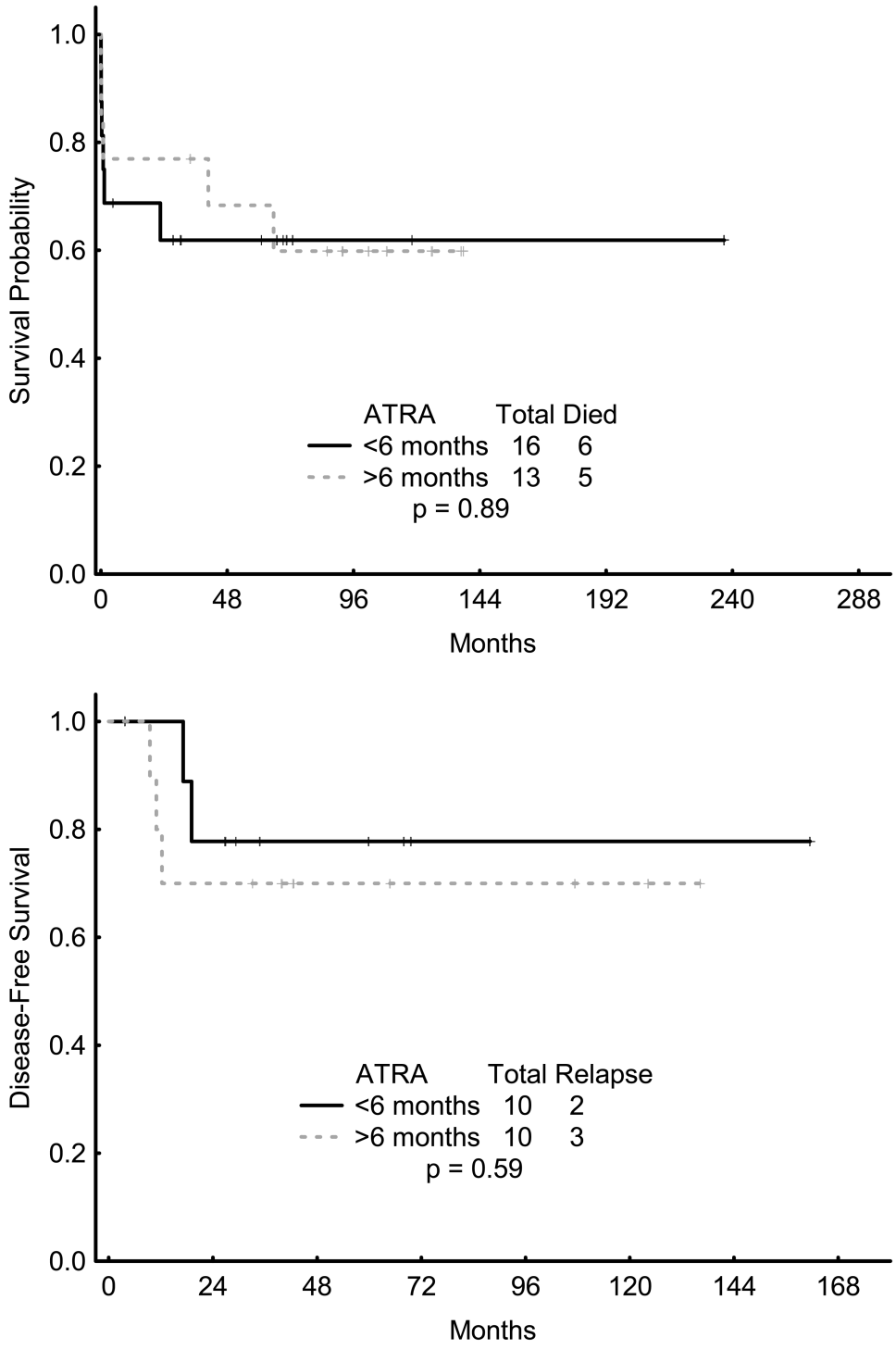


**Fig 3.**

Overall survival (A) and disease-free survival (B) among APL patients who received ≤6 months of ATRA therapy and those that received >6 months of ATRA therapy We did not identify a meaningful difference in overall survival and disease-free survival among patients

who received ≤6 months of ATRA therapy and those that received >6 months of ATRA therapy. APL, acute promyelocytic leukaemia; ATRA, all-trans retinoic acid.

## Table I

### Patient characteristics

| Parameter | | WBC ≥ 50 × $10^9$/l n (%)/median [range] | WBC < 50 × $10^9$/l n (%)/median [range] | *P* value |
|---|---|---|---|---|
| **N** | | **29** | **213** | |
| **Age (years)** | | 43 [13-77] | 46 [13-84] | 0.26 |
| **Bone marrow blasts (%)** | | 91.5 [77-97] | 75 [19-96] | <0.001 |
| **WBC (× $10^9$/l)** | | 87.6 [50.1-195.0] | 2.7 [0.4-47.4] | <0.001 |
| **Haemoglobin (g/l)** | | 87 [59-140] | 89 [38-151] | 0.77 |
| **Platelets (× $10^9$/l)** | | 26 [10-124] | 38 [3-261] | 0.05 |
| **Cytogenetics** | Isolated t(15:17) | 25 (86) | 189 (89) | |
| | Others | 3 (10) | 15 (7) | 0.54 |
| | Not done | 1 (3) | 9 (4) | |
| ***PML-RARA*** | Long transcript | 2 (7) | 89 (42) | |
| | Short transcript | 18 (62) | 72 (34) | 0.001 |
| | Variable | 1 (3) | 1 (1) | |
| | Not done | 8 (28) | 50 (23) | |
| **DIC parameters** | Fibrinogen | 242 [99-662] | 250 [65-700] | 0.81 |
| | PT | 16.6 [12.6-24.2] | 14.7 [10.2-23.2] | <0.001 |
| | PTT | 25 [20.8-36.7] | 26.8 [17.3-70.4] | 0.04 |
| **AHD** | | 4 (14) | 49 (23) | 0.26 |
| **Prior chemotherapy/radiation** | | 3 (10) | 31 (15) | 0.57 |
| ***FLT3* status** | Mutated | 9 (31) | 40 (19) | |
| | Wild type | 0 | 59 (28) | <0.01 |
| | Not performed | 20 (69) | 114 (53) | |

Abbreviations: APL, acute promyelocytic leukaemia; WBC, white blood cell count; DIC, disseminated intravascular coagulation; PT, prothrombin time; PTT, partial thromboplastin time; AHD, antecedent haematological disorder.

## Table II

**3-year OS for patients with APL and WBC ≥ 50 × $10^9$/l by patient characteristics**

| Characteristics | n (%) | 3-year survival (%) | *P-value* |
|---|---|---|---|
| **Age** | | | |
| **≤65 years** | 24 | 79 | 0.12 |
| **>65 years** | 5 | 20 | |
| **Gender** | | | |
| **Male** | 13 | 69 | 0.94 |
| **Female** | 16 | 68 | |
| **Cytogenetics** | | | |
| **t(15;17) alone** | 17 | 88 | 0.12 |
| **t(15;17) + Other** | 6 | 50 | |
| **Clinical Stasis** | | | |
| **Yes** | 23 | 70 | 0.58 |
| **No** | 6 | 67 | |
| **WBC** | | | |
| **≤100 × $10^9$/l** | 17 | 77 | 0.64 |
| **>100 × $10^9$/l** | 12 | 57 | |
| **Platelets** | | | |
| **≤20 × $10^9$/l** | 11 | 62 | 0.9 |
| **>20 × $10^9$/l** | 18 | 72 | |
| **≤40 × $10^9$/l** | 26 | 65 | 0.16 |
| **>40 × $10^9$/l** | 3 | 100 | |
| **Fibrinogen** | | | |
| **≤2 g/l** | 11 | 64 | 0.43 |
| **>2 g/l** | 16 | 75 | |
| **Leukapheresis** | | | |
| **Yes** | 11 | 73 | 0.64 |
| **No** | 18 | 67 | |
| **Regimen** | | | |
| **ATRA/ATO** | 15 | 100 | **0.002** |
| **Non-ATRA/ATO** | 14 | 35 | |

Abbreviations: OS, overall survival; APL, acute promyelocytic leukaemia; WBC, white blood cell count; ATRA, all-trans retinoic acid; ATO, arsenic trioxide.

## Table III
### Comparison of outcomes of patients with APL

| Parameter | APL with WBC ≥ 50 × $10^9$/l, n=29 | APL with WBC < 50 × $10^9$/l, n=213 | *P* value |
|---|---|---|---|
| **Early mortality (≤4 weeks)** | 7 (24%) | 20 (9%) | **0.018** |
| **Median OS (months, range)** | NR | NR | - |
| **3-year OS rate (%)** | 69% | 80% | 0.2 |
| **Median DFS (months, range)** | NR | NR | - |
| **3-year DFS (%)** | 74% | 92% | 0.057 |

Abbreviations: APL, acute promyelocytic leukaemia; WBC, white blood cell count; OS, overall survival; DFS, disease-free survival; NR, no response.

**Table IV**

Prior reports of leukapheresis in patients with acute myeloid leukaemia.

| Study | Number of patients who underwent leukapheresis | Median WBC at time of presentation (× $10^9$/l) | Median number of leukapheresis sessions | Chemotherapy regimens | Median overall survival |
|---|---|---|---|---|---|
| Thiebaut, *et al* (2000) | 53 | 160 | 1 | Anthracycline + cytarabine +/- etoposide +/- 6-MP | 8 months |
| Giles, *et al* (2001) | 71 | 116 | 1 | (1) Idarubicin + cytarabine +/- G-CSF or lisofylline<br>(2) Fludarabine + cytarabine +/- either idarubicin and/or G-CSF or ATRA or<br>(3) Topotecan + cytarabine +/- cyclophosphamide. | 11.5 months |
| Bug, *et al* (2007) | 25 | 186 | 1 | Idarubicin + etoposide + cytarabine, or cytarabine + amsacrine | 6.5 months |
| DeSantis, *et al* (2011) | 15 | 200 | 2 | Anthracycline + cytarabine | 10 days |
| Chang *et al* (2007) | 38 | Not available | 1 (+/- cranial irradiation) | Anthracycline + cytarabine | 1.5 months. |

Abbreviations: WBC, white blood cell count; 6-MP, 6-mercaptopurine; G-CSF, granulocyte-colony stimulating factor; ATRA, all-trans-retinoic-acid.