7 Prognostic Factors in Acute Promyelocytic Leukemia

Javier de la Serna, Pau Montesinos, and Miguel A. Sanz

Introduction

The prognosis of acute promyelocytic leukemia (APL) has extraordinarily improved since the introduction of anthracycline-based chemotherapy [1], but especially after the advent of all-*trans* retinoic acid (ATRA) [2] and arsenic trioxide (ATO) [3]. In fact, following the optimization of frontline therapy with the use of a simultaneous combination of ATRA and anthracycline-based chemotherapy, primary resistance during induction therapy has virtually disappeared, with death during induction remaining as the only cause of failure [4]. In addition, using ATRA and anthracycline-based approaches, both in induction and post-remission therapy, several groups have reported a dramatic reduction in relapse rates to roughly 10% of patients who achieve first complete remission (CR) [5–9]. Such improvements in APL prognosis have also been reported with alternative treatments based on the addition of ATO to the conventional ATRA plus chemotherapy combination [10–15], but also with the combination of ATRA and ATO without or with minimal use of chemotherapy [16, 17].

Death during induction therapy and relapse are currently the major events involved in therapeutic failures in patients with APL. However, other less frequent but important late events, such as death while in first CR during post-remission therapy and the development of therapy-related neoplasms, have also an impact on patient outcome and, therefore, should be taken into account to design curative strategies for patients with APL. In this regard, the study of key characteristics associated with these events (prognostic factors) has always been considered a matter of great interest, since their recognition would translate into therapeutic improvements. In fact, over the past two decades, most therapeutic approaches have been designed following risk-adapted strategies in order to optimize the therapeutic efficacy by minimizing side effects, particularly in those patients considered at low risk of developing a given event.

In this chapter, in addition to review the prognostic factors of classical composite end points, such as CR rate, disease-free survival

J. de la Serna, M.D.
Department of Hematology, Hospital Universitario 12 de Octubre, Madrid, Spain

P. Montesinos, M.D., Ph.D.
Department of Hematology, Hospital Universitari i Politècnic La Fe, Valencia, Spain

Centro de Investigación Biomédica en Red de Cáncer, Instituto Carlos III, Madrid, Spain

M.A. Sanz, M.D. (✉)
Department of Medicine, Hospital Universitari i Politecnic La Fe, University of Valencia, Valencia, Spain

Centro de Investigacion Biomedica en Red de Cancer, Instituto Carlos III, Madrid, Spain
e-mail: msanz@uv.es

O. Abla et al. (eds.), *Acute Promyelocytic Leukemia*, https://doi.org/10.1007/978-3-319-64257-4_7

(DFS), event-free survival (EFS), and overall survival (OS), we will also discuss those patient and disease characteristics associated with specific events which determine the previously mentioned composite end points. Thus, for example, together with the recognition of prognostic factors of induction response, typically analyzed as a binary end point, the identification of predictive factors of the different causes of induction failure would provide an added value. The recognition of specific predictors of the different causes of induction failure would allow the design of tailored approaches according to the specific risk of death due to bleeding, infection, or differentiation syndrome (DS). Furthermore, assuming that the effectiveness of treatment is a major determinant in prognosis, this issue should be analyzed today in the context of the two principal therapeutic approaches currently used for APL, such as ATRA plus chemotherapy-based and ATRA plus ATO-based therapy.

Prognostic Factors of Induction Response

Classically, prognostic factors of induction response have been assessed considering only the binary option of CR versus induction failure, considering the latter as a whole. Table 7.1 shows the prognostic factors found in most representative series of patients with APL treated using modern therapeutic approaches. To analyze prognostic factors of induction response, the vast majority of these studies considered all causes of induction death as a single event.

The prognostic impact of WBC counts on induction response has been demonstrated in virtually all series (Table 7.1). Both in patients treated with ATRA plus anthracycline-based chemotherapy [4, 7, 18–24] and in those managed with ATO-based treatment [25, 26], WBC count is associated with a higher risk of induction failure. The cutoff point generally used for WBC count is 10×10^9/L at presentation. The prognostic impact of age is also an almost constant finding in series including sufficient patients with a wide age range, with older patients being those with a higher risk of induction failure.

Other patient and disease characteristics have also been reported less consistently as prognostic factors of induction failure. The presence of coagulopathy, abnormal serum creatinine, and albumin levels at presentation have been recognized as prognostic factors in two large series [4, 24].

A higher induction mortality rate in CD56-positive patients was originally suggested in a study based on a small series of patients not receiving a state-of-the-art treatment [27]. In a large study including 651 patients homogeneously treated with AIDA regimen [28], a multivariable analysis was able to demonstrate an independent prognostic value of CD56 positivity (≥20% of leukemic cells) not only for relapse (which will be discussed below) but also as predictor of induction death. Despite of the association of CD56 expression with other recognized adverse factors for induction response [4], this phenotypic feature was selected to enter into the regression model together with abnormal creatinine level, WBC count greater than 10×10^9/L, age older than 60 years, male sex, and ECOG more than 1 [28].

Carriers of a functional variant in the core promoter of the CD95 cell death receptor gene, who were enrolled in the United Kingdom Medical Research Council (MRC) AML 12 trial, were more likely to die during remission induction and had a significantly worse overall survival [29]. To the best of our knowledge, this finding has not yet been validated in other studies.

A relationship between additional chromosomal abnormalities (ACA) and induction outcome in APL was first suggested in the 1990s in two retrospective studies carried out in small series of patients mostly treated with chemotherapy alone [30, 31]. More recently, also in a small cohort of patients managed with ATRA plus anthracycline-based induction therapy, the German AML Study Group [20] found that patients dying during induction therapy had significantly higher likelihood of trisomy 8 or abn(7q). However, other larger studies in patients with APL managed with state-of-the-art

Table 7.1 Studies of prognostic factors of induction response with modern induction therapy

Study	Group	Treatment	No. of patients	Age, median (range)	CR rate	Induction death rate	Prognostic factors identified in multivariable analysis
Fenaux et al. [22]	European APL	ATRA + Dauno/AraC	413	46 (1–83)	92	7	WBC count Age
Lo-Coco et al. [7]	GIMEMA	AIDA	1081	38–41 (18–81)	94	6	WBC count Platelets count Age
Sanz et al. [21]	PETHEMA	AIDA	426	39 (2–81)	90	9	WBC count Age
de la Serna et al. [4]	PETHEMA	AIDA	732	40 (2–83)	91	9	Creatinine level WBC count PB blast count Age Sex
Schlenk et al. [20]	AMLSG	AIDA	75	43 (16–60)	76 (+15)	9	WBC count Cytogenetics
Burnett et al. [18]	MRC	ATRA + Dauno/AraC ± other	120	NA	87	12	WBC count Age
Gale et al. [47]	MRC	ATRA + Dauno/AraC ± other	203	37 (1–60)	84	13	WBC count
Lengfelder et al. [23]	GAMLCG	ATRA + TAD/HAM	142	40 (16–60)	92	8	WBC count
Rego et al. [24]	ICAL	ATRA + Dauno	180	34 (15–73)	85	15	WBC count Coagulopathy Creatinine level Albumin level
Ghavamzadeh et al. [25]	Single institution	ATO	197	29 (11–71)	86	15	WBC count
Ravandi et al. [26]	Single institution	ATRA + ATO ± GO	81	47 (14–81)	92	8	WBC count

Table 7.2 Prognostic factors of specific causes of induction death with modern induction therapy

					Prognostic factors identified in multivariable analysis		
Study	Group	No. of patients	CR rate	Induction death rate	Induction death due to bleeding	Induction death due to infection	Induction death due to DS
Di Bona et al. [19]	GIMEMA	499	92	8	Peripheral blast count[a] Hemorrhagic score[a]	Not analyzed	Not analyzed
de la Serna et al. [4]	PETHEMA	732	91	9	Creatinine level PB blast count Coagulopathy	Age Sex Fever	ECOG score Albumin level
De Botton et al. [36]	European APL	413	92	7	Not analyzed	Not analyzed	Not found
Yanada et al. [72]	JALSG	279	95	5	Fibrinogen level[b] WBC count[b] PS score[b]	Not analyzed	Not analyzed

[a]Prognostic factors of early death (<day 10)
[b]Prognostic factors of severe hemorrhage (half of them were not lethal)

treatments have not found such impact on induction outcome [32–35].

Some additional studies shown in Table 7.2 have analyzed separately specific induction outcomes instead of induction response as a whole. A study of the Italian GIMEMA group reported a significant association between peripheral blast counts, hemorrhagic score and early death (<day 10) [19]. On the other hand, a study of the European APL group was unable to find any pretreatment feature associated with mortality due to DS [36]. In contrast, a larger study of the PETHEMA-HOVON groups identified ECOG score >1 and low albumin levels to be associated with an increased risk of death due to this syndrome [4]. In addition, this analysis identified specific and distinct pretreatment set of characteristics associated with an increased risk of death due to hemorrhage (abnormal creatinine level, increased peripheral blast counts, and presence of coagulopathy) and infection (age > 60 years, male gender, and fever at presentation). This study provided clinically relevant information for practice and for designing risk-adapted strategies focused on reducing mortality from hemorrhage, infection, and DS during early treatment phases of APL.

An increased body mass index at diagnosis has also been associated with a higher risk of developing DS in APL patients treated with AIDA protocols, but not with an increased mortality due to this syndrome [37–39].

Although many prognostic factors that were recognized in the pre-ATO era have now been challenged in the era of ATO therapy [40], there is enough evidence demonstrating a poorer induction outcome for patients with elevated WBC count also when they are treated with ATO-based regimens. In fact, most current ATO-based approaches include the addition of anthracyclines or gemtuzumab ozogamicin for induction therapy in patients presenting hyperleukocytosis. The prognostic impact on induction outcome of other presenting features, such as age, gender, coagulopathy, CD56 expression, creatinine, and albumin levels, among others, should be confirmed in large series treated with ATO-based regimens.

Prognostic Factors of Induction Response in Children

A large retrospective study [41] has recently focused on determining the incidence and predictors of thrombo-hemorrhagic deaths during induction therapy in children and adolescents with APL treated with ATRA and chemotherapy by several international groups. This study has shown an incidence of early thrombo-hemorrhagic deaths of 4.7%, with CNS hemorrhage being the most

common site for this lethal complication. High WBC (>10 × 10^9/L) and high PB blast (>30 × 10^9/L), M3v morphological subtype and black ethnicity were identified as predictors of hemorrhagic death during induction therapy in univariable analysis. However, in multivariable analysis, only high WBC count retained an independent prognostic value together with obesity, defined as a body mass index ≥95 percentile for age. As far as we know, no other studies have been reported regarding prognostic factors of induction outcomes in children.

Prognostic Factors of Post-remission Outcomes

Prognostic factors of specific post-remission outcomes, such as relapse, death during remission, and development of therapy-related myeloid neoplasms (t-MN) have been analyzed in only a marginal way in the majority of studies in APL. In addition, these events have generally been considered as a whole in a context of composite end points, such as EFS, DFS, and OS. However, the interpretation of composite end points with coexisting competing risks can reduce precision in estimating not only the probability of the occurrence of primary events [42], but also the prognostic factors involved in these adverse events. Therefore, in this chapter, we will review the prognostic factors implicated in the classical composite end points (EFS, DFS, OS), but also those found in the most important primary events (relapse, death during remission, t-MN).

Predictors of Composite End Points

Similar to induction response, the prognostic impact of WBC counts on the risk of relapse is universally accepted, regardless of the type of treatment used, with a higher risk for patients with WBC counts greater than 10 × 10^9/L at presentation. The prognostic value of WBC counts has a variable impact on composite end points in which relapse is one of the events directly considered, such as EFS, DFS, and RFS. Despite the indirect effect that relapse may have on OS, the impact of WBC counts on this end point may not appear evident due to the high antileukemic efficacy of salvage therapy in APL. In this regard, the score defined after a joint GIMEMA and PETHEMA study [43], based on the presenting WBC and platelet counts, has been regarded as the mainstay for risk stratification in most APL clinical trials, being so widely adopted because of its simplicity and reproducibility.

Other prognostic factors, such as male gender and morphologic classification, M3V, and classical M3 APL, have occasionally been associated with post-remission outcomes, but they lose their prognostic value when adjusted for the WBC or relapse risk score [44].

In general, prognostic factors different to WBC and relapse risk score have not been incorporated into decision-making, with the exception, to the best of our knowledge, of age and CD56 expression. Using a 20% cutoff point of leukemic promyelocytes expressing CD56 in three subsequent PETHEMA trials with AIDA-derived approaches (LPA96, LPA99, and LPA2005 trials), CD56 was found to be an independent prognostic factor not only for induction death, as previously mentioned, but also for relapse [28]. Subsequent to this study, PETHEMA trials have incorporated CD56 expression for refining risk stratification. In particular, in the context of risk-adapted consolidation therapy, patients classified according to relapse-risk score [43] are now upgraded one level when CD56 is positive. Thus, low- and intermediate-risk CD56-positive patients are treated for consolidation as intermediate- and high-risk patients, respectively.

It has been suggested that various molecular features could be useful to predict outcomes in APL, but most of these molecular predictors have still not been validated. In addition, logistic and technical issues have hampered a generalized use of these sophisticated tools so far.

The prognostic impact of FLT3 mutations has been widely analyzed in the context of ATRA plus chemotherapy with controversial results [45–55]. The methodological heterogeneity of these studies regarding the sample size, diversity of treatments, use or not of multivariable analysis, as well as the

variables and end points analyzed, make it difficult to obtain reliable and definitive conclusions. The vast majority of these studies, however, have revealed a strong association between leukocytosis and FLT3 mutations. In this regard, the results reported in a large cohort by the PETHEMA-HOVON group [52] showed that FLT3-ITD status was removed from the regression equation when the WBC count was included in the multivariable analysis, suggesting that the adverse outcome of this mutation is attributable to its relationship with elevated WBC count. Furthermore, this study was unable to demonstrate the adverse prognostic impact that had previously been reported for the FLT3-D835 mutation [47] and the ratio and length of FLT3-ITD mutations [48].

The prognostic impact of FLT3 mutations has been less often studied in APL patients treated with ATO-based regimens. In this regard, neither the Australasian Leukaemia and Lymphoma Group [13] nor the North American Intergroup [35], both using ATRA, ATO, and chemotherapy, found differences in any post-remission outcome by FLT3 status. The Italian-German APL0406 randomized trial, using ATRA plus ATO without chemotherapy, but restricted to non-high risk patients, also failed to detect any impact of FLT3 status on outcome [55]. Finally, an elegant study carried out on 535 newly diagnosed APL patients treated with an ATRA/ATO-based protocol at Shanghai Institute of Hematology and affiliated centers [56] deserves special mention. This study showed that FLT3-ITD or FLT3-TKD, N-RAS, and WT1 mutations were the three most common additional gene mutations (15.8%, 4.5%, and 4.7%, respectively), but none of them had a significant impact on OS and DFS. In contrast, mutations of epigenetic modifier genes (EMG), such as DNMT3A (0.3%), TET2 (4.5%), IDH1 (0.4%), IDH2 (0.2%), and ASXL1 (1.6%), which together account for 6.5%, showed an independent prognostic value for DFS in multivariable analysis, together with the relapse risk score [43], whereas for OS this score was the only factor indicating poor prognosis.

In addition to mutations, the expression of several genes has also been explored as prognostic molecular markers in APL. Three subsequent studies of the German AML Cooperative Group (AMLCG) [57–59], carried out on relatively small cohorts of patients enrolled in two consecutive trials, showed that the expression levels of three different genes, BAALC [57], ERG [58], and WT1 [59] had an independent prognostic value for APL risk stratification. Based on these studies, a molecular risk score, which includes the expression level of the three genes, has been developed [60]. This integrative risk score was able to divide patients into two groups with statistically significant differences in OS, RFS, and CIR. The prognostic value of the expression of other genes has also been reported. A study carried out on patients enrolled in the International Consortium of APL trial showed that a low expression of KMT2E is associated with a shorter OS [61] and a higher DNp73/TAp73 RNA expression ratio with a lower OS and DFS, as well as higher risk of relapse in patients with APL. Finally, a Spanish group has reported that low PRAME expression defines a subgroup of APL patients with a short RFS [62].

Based on a large cohort of 187 PML/RARA-positive APL patients enrolled in three subsequent trials of the North American Leukemia Intergroup, it has been reported that telomere length (TL), in particular delta TL, defined as TL at remission minus TL at diagnosis, is a strong predictor of OS [63]. These findings, as well as those previously mentioned regarding mutations and gene expression, warrant prospective confirmation studies.

Several studies carried out on patients managed with state-of-the-art treatments were unable to demonstrate an independent prognostic impact of the presence of additional chromosomal abnormalities (ACA) on any post-remission outcome [32–35], with the exception of a recent study from the North American Intergroup [35]. In this study, the presence of a complex karyotype (≥2 ACAs) was strongly associated with an inferior OS independently of the post-remission treatment arm, even when ATO was given for consolidation therapy. This novel observation deserves further investigation in larger cohorts of patients treated with either chemotherapy-based or ATO-based state-of-the-art treatments.

Predictors of Specific Post-remission Events

The limitations of using composite end points for the analysis of prognostic factors have been widely discussed in the literature [42], but any discussion is outside the scope of this chapter. The precise estimate of post-remission events of primary interest, such as relapse and therapy-related adverse events, including death during remission and development t-MN, is affected by competing risks when analyzed using composite end points. Few studies have analyzed specifically these post-remission events taking into account competing risks.

Relapse

There is a general agreement that the impact of WBC count on prognosis of APL patients is not only restricted to induction response, mainly associated with induction deaths due to hemorrhages, but also is associated with the risk of relapse. Therefore, with EFS, DFS, and OS, the three meaningful composite end points in which relapse and death during remission have a considerable weight. Although some previous studies [18, 64, 65] have found a significantly higher incidence of relapse for patients with high WBC counts, the crucial prognostic value of this factor to predict relapse was definitively established in a joint GIMEMA and PETHEMA study [43]. In this study, multivariable analysis resulted in a simplified predictive model for relapse-free survival that has been widely adopted around the world. This model permits the identification of the following patient categories: (1) low-risk group, presenting WBC count below or equal to 10×10^9/L and platelet count above 40×10^9/L; (2) intermediate-risk group, presenting WBC and platelet counts below or equal to 10×10^9/L and 40×10^9/L, respectively; and (3) high-risk group, presenting WBC count greater than 10×10^9/L.

The expression of CD56 has also been defined as a predictor of relapse. This has been suggested in previous studies [27, 66, 67], and confirmed in a large study of the PETHEMA-HOVON group [28]. In addition to relapse risk score, the expression of CD56 using a 20% cutoff level is also an independent and accurate predictor for relapse in patients with APL treated with ATRA and anthracycline-based regimens. CD56-positive APL also showed a significantly higher risk of extramedullary relapse. Interestingly, CD56 positivity, with a prevalence of 11% of newly diagnosed patients, is correlated with the BCR3 isoform and the co-expression of other surface antigens, such as CD2, CD34, HLA-DR, and CD7 [28]. An increased body mass index at diagnosis has also been associated with a higher risk of disease relapse [38], but this finding has not yet been validated in larger series.

Several molecular markers have also been reported to be associated with relapse risk. This is the case of the expression of the gene PRAME, considered a good predictor of RFS [62], and an integrative risk score that includes the expression of three genes (BAALC, ERG, and WT1) [60], which are able to identify two groups with statistically significant differences in RFS and cumulative incidence of relapse.

Finally, in contrast to the lack of clinical value of molecular assessment of PML/RARA performed at the end of induction, it is widely accepted that patients with persistent or recurrent disease at the molecular level at any stage after completion of consolidation will invariably relapse, unless additional therapy is given. In contrast, continued persistent molecular negativity by RT-PCR or RQ-PCR is associated with a low relapse risk.

Central Nervous System Relapse

To the best of our knowledge, only two large studies [68, 69] have specifically analyzed the prognostic factors involved in extramedullary relapse, with particular reference to CNS relapse. In multivariable analysis, a study of the European APL group [68] found that only a high WBC count (cutoff point 10×10^9/L) is independently associated with CNS relapse, whereas a PETHEMA-HOVON study [69] found the occurrence of cerebral hemorrhage during induction and the relapse risk score, which is a composite of WBC

and platelet counts [43], are the most valuable predictors of CNS relapse.

Regarding other potential risk factors for CNS relapse, some authors have suggested that FLT3-ITD mutations, which correlate with leukocytosis [47], and an increased expression of adhesion molecules, such as CD56, can promote leukemic infiltration in CNS and other extramedullary sites [28]. In fact, CD56 APL had a significantly higher risk of extramedullary relapse in a large series of patients included in several PETHEMA-HOVON trials [28].

Development of Therapy-Related Myeloid Neoplasms

Regarding risk factors of development of t-MN in APL, to our knowledge, only one study has addressed this issue [70]. The univariable analysis in this PETHEMA-HOVON study showed the following characteristics were associated with the development of t-MN: older age (cutoff 35 years), lower relapse risk score, and higher platelet count (cutoff 40 × 10^9/L). Multivariable analysis, however, only identified age and relapse risk score as independent prognostic factors for t-MN. There is no clear explanation for the apparent paradoxical finding of a higher risk of developing t-MN in patients with a lower risk of relapse, but it has been speculated that a greater frequency of competing events in patients with higher risk APL, particularly relapse and death in remission, decreases the chance of developing t-MN while in first CR [70].

Although a potential relationship between dose intensity of topoisomerase II inhibitors or intercalating agents and incidence of t-MN has been suggested, data from this PETHEMA-HOVON study [70] does not clearly support this hypothesis, since the increased risk of t-MN was observed in lower-risk APL patients, who overall were less heavily treated. Therefore, it is not clear whether anthracycline dose reduction, or even its replacement by arsenic trioxide, would be effective to decrease the incidence of t-MN.

Death During First Remission

Apart from the classical composite end points, such as OS, EFS, and DFS, in which death during first remission is one of the events considered, a precise estimate of this post-remission event of primary interest has hardly been analyzed. Nevertheless, it is generally accepted that death during first remission is mainly associated with age and comorbidities, along with dose intensity of post-remission therapy. It should be noted, however, that some deaths occur off-therapy due to causes not associated directly with therapy-related toxicity. The unquestionable impact of age on non-relapse mortality has led many groups to design age-adapted trials. In this regard, a recent report of the PETHEMA group [71] showed a significant improvement in long-term outcomes, which were mainly attributed to a decrease in hematologic toxicity and toxic death rates, using a less intensive frontline regimen with ATRA and anthracycline monochemotherapy in elderly patients with APL.

Whether non-relapse mortality can be reduced with age-adapted approaches, not only by decreasing dose intensity of chemotherapy in elderly patients, but also replacing chemotherapy by ATO, is still an open issue warranting further research.

Conclusions

The identification of prognostic factors has always been considered a matter of great interest in APL, since their recognition would allow the use of risk-adapted strategies aimed at optimizing the therapeutic efficacy and minimizing treatment-related toxicity, which in turn would translate into better outcomes. Early deaths during induction therapy and relapse are currently the most frequent events involved in therapeutic failures; however deaths in CR during post-remission therapy and even off-therapy, as well as the development of therapy-related neoplasms, are other important events with negative impact on outcome.

Several patient- and disease-related characteristics have been recognized as prognostic factors, but only age and WBC count, as well

as a composite risk score including WBC and platelet counts to predict relapse and other surrogate end points, have been widely used for risk-adapted stratification in clinical trials. In addition to WBC count and the risk score, the expression of CD56 and the occurrence of cerebral hemorrhage during induction have been identified as independent and accurate predictors of hematologic and CNS relapse, respectively. Accordingly, patients included in the most recent risk-adapted PETHEMA trials are upgraded one level based on the relapse risk score when CD56 is positive, whereas those who develop a cerebral hemorrhage during induction are given systematic CNS prophylaxis. Other characteristics, such as an increased BMI, presence of additional chromosomal abnormalities, and mutational status and expression profiles of a variety of genes have also been recognized as independent prognostic factors. However, most of these predictors have not yet been validated in large and independent series.

It should be noted that the body of knowledge acquired over the last two decades on prognostic factors in APL has mainly been obtained in the context of ATRA plus chemotherapy-based regimens, while the impact of these factors after the incorporation of ATO in frontline therapy has not been established. Large studies with prolonged follow-up will be necessary to identify the best predictors of outcome in APL patients receiving ATO containing regimens, although it appears that age and WBC count will continue to play a key role.

References

1. Bernard J, Weil M, Boiron M, et al. Acute promyelocytic leukemia: results of treatment by daunorubicin. Blood. 1973;41:489–96.
2. Huang ME, Ye YC, Chen SR, et al. Use of all-trans retinoic acid in the treatment of acute promyelocytic leukemia. Blood. 1988;72:567–72.
3. Shen ZX, Chen GQ, Ni JH, et al. Use of arsenic trioxide (As2O3) in the treatment of acute promyelocytic leukemia (APL): II. Clinical efficacy and pharmacokinetics in relapsed patients. Blood. 1997;89:3354–60.
4. de la Serna J, Montesinos P, Vellenga E, et al. Causes and prognostic factors of remission induction failure in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and idarubicin. Blood. 2008;111:3395–402. https://doi.org/10.1182/blood-2007-07-100669.
5. Adès L, Chevret S, Raffoux E, et al. Is cytarabine useful in the treatment of acute promyelocytic leukemia? Results of a randomized trial from the European Acute Promyelocytic Leukemia Group. J Clin Oncol. 2006;24:5703–10. https://doi.org/10.1200/JCO.2006.08.1596.
6. Asou N, Kishimoto Y, Kiyoi H, et al. A randomized study with or without intensified maintenance chemotherapy in patients with acute promyelocytic leukemia who have become negative for PML-RARalpha transcript after consolidation therapy: the Japan Adult Leukemia Study Group (JALSG) APL97 study. Blood. 2007;110:59–66. https://doi.org/10.1182/blood-2006-08-043992.
7. Lo-Coco F, Avvisati G, Vignetti M, et al. Front-line treatment of acute promyelocytic leukemia with AIDA induction followed by risk-adapted consolidation for adults younger than 61 years: results of the AIDA-2000 trial of the GIMEMA Group. Blood. 2010;116:3171–9. https://doi.org/10.1182/blood-2010-03-276196.
8. Sanz MA, Montesinos P, Rayón C, et al. Risk-adapted treatment of acute promyelocytic leukemia based on all-trans retinoic acid and anthracycline with addition of cytarabine in consolidation therapy for high-risk patients: further improvements in treatment outcome. Blood. 2010;115:5137–46. https://doi.org/10.1182/blood-2010-01-266007.
9. Burnett AK, Hills RK, Jovanovic JV, et al. Inclusion of chemotherapy in addition to anthracycline in the treatment of acute promyelocytic leukaemia does not improve outcomes: results of the MRC AML15 trial. Leukemia. 2013;27:843–51. https://doi.org/10.1038/leu.2012.360.
10. Hu J, Liu Y-F, Wu C-F, et al. Long-term efficacy and safety of all-trans retinoic acid/arsenic trioxide-based therapy in newly diagnosed acute promyelocytic leukemia. Proc Natl Acad Sci U S A. 2009;106:3342–7. https://doi.org/10.1073/pnas.0813280106.
11. Powell BL, Moser B, Stock W, et al. Arsenic trioxide improves event-free and overall survival for adults with acute promyelocytic leukemia: North American Leukemia Intergroup Study C9710. Blood. 2010;116:3751–7. https://doi.org/10.1182/blood-2010-02-269621.
12. Gore SD, Gojo I, Sekeres MA, et al. Single cycle of arsenic trioxide-based consolidation chemotherapy spares anthracycline exposure in the primary management of acute promyelocytic leukemia. J Clin Oncol. 2010;28:1047–53. https://doi.org/10.1200/JCO.2009.25.5158.
13. Iland HJ, Bradstock K, Supple SG, et al. All-trans-retinoic acid, idarubicin, and IV arsenic trioxide as initial therapy in acute promyelocytic leukemia (APML4). Blood. 2012;120:1570–80; quiz 1752. https://doi.org/10.1182/blood-2012-02-410746.

14. Iland HJ, Collins M, Bradstock K, et al. Use of arsenic trioxide in remission induction and consolidation therapy for acute promyelocytic leukaemia in the Australasian Leukaemia and Lymphoma Group (ALLG) APML4 study: a non-randomised phase 2 trial. Lancet Haematol. 2015;2:e357–66. https://doi.org/10.1016/S2352-3026(15)00115-5.
15. Zhu H-H, Wu D-P, Jin J, et al. Long-term survival of acute promyelocytic leukaemia patients treated with arsenic and retinoic acid. Br J Haematol. 2016;174:820–2. https://doi.org/10.1111/bjh.13809.
16. Lo-Coco F, Avvisati G, Vignetti M, et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med. 2013;369:111–21. https://doi.org/10.1056/NEJMoa1300874.
17. Burnett AK, Russell NH, Hills RK, et al. Arsenic trioxide and all-trans retinoic acid treatment for acute promyelocytic leukaemia in all risk groups (AML17): results of a randomised, controlled, phase 3 trial. Lancet Oncol. 2015;16:1295–305. https://doi.org/10.1016/S1470-2045(15)00193-X.
18. Burnett AK, Grimwade D, Solomon E, et al. Presenting white blood cell count and kinetics of molecular remission predict prognosis in acute promyelocytic leukemia treated with all-trans retinoic acid: result of the Randomized MRC Trial. Blood. 1999;93:4131–43.
19. Di Bona E, Avvisati G, Castaman G, et al. Early haemorrhagic morbidity and mortality during remission induction with or without all-trans retinoic acid in acute promyelocytic leukaemia. Br J Haematol. 2000;108:689–95.
20. Schlenk RF, Germing U, Hartmann F, et al. High-dose cytarabine and mitoxantrone in consolidation therapy for acute promyelocytic leukemia. Leukemia. 2005;19:978–83. https://doi.org/10.1038/sj.leu.2403766.
21. Sanz MA, Martín G, González M, et al. Risk-adapted treatment of acute promyelocytic leukemia with all-trans-retinoic acid and anthracycline monochemotherapy: a multicenter study by the PETHEMA group. Blood. 2004;103:1237–43. https://doi.org/10.1182/blood-2003-07-2462.
22. Fenaux P, Chastang C, Chevret S, et al. A randomized comparison of all transretinoic acid (ATRA) followed by chemotherapy and ATRA plus chemotherapy and the role of maintenance therapy in newly diagnosed acute promyelocytic leukemia. The European APL Group. Blood. 1999;94:1192–200.
23. Lengfelder E, Haferlach C, Saussele S, et al. High dose ara-C in the treatment of newly diagnosed acute promyelocytic leukemia: long-term results of the German AMLCG. Leukemia. 2009;23:2248–58. https://doi.org/10.1038/leu.2009.183.
24. Rego EM, Kim HT, Ruiz-Argüelles GJ, et al. Improving acute promyelocytic leukemia (APL) outcome in developing countries through networking, results of the International Consortium on APL. Blood. 2013;121:1935–43. https://doi.org/10.1182/blood-2012-08-449918.
25. Ghavamzadeh A, Alimoghaddam K, Rostami S, et al. Phase II study of single-agent arsenic trioxide for the front-line therapy of acute promyelocytic leukemia. J Clin Oncol. 2011;29:2753–7. https://doi.org/10.1200/JCO.2010.32.2107.
26. Ravandi F, Estey E, Jones D, et al. Effective treatment of acute promyelocytic leukemia with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab ozogamicin. J Clin Oncol. 2009;27:504–10. https://doi.org/10.1200/JCO.2008.18.6130.
27. Murray CK, Estey E, Paietta E, et al. CD56 expression in acute promyelocytic leukemia: a possible indicator of poor treatment outcome? J Clin Oncol. 1999;17:293–7. https://doi.org/10.1200/jco.1999.17.1.293.
28. Montesinos P, Rayón C, Vellenga E, et al. Clinical significance of CD56 expression in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and anthracycline-based regimens. Blood. 2011;117:1799–805. https://doi.org/10.1182/blood-2010-04-277434.
29. Sunter NJ, Scott K, Hills R, et al. A functional variant in the core promoter of the CD95 cell death receptor gene predicts prognosis in acute promyelocytic leukemia. Blood. 2012;119:196–205. https://doi.org/10.1182/blood-2011-04-349803.
30. Slack JL, Arthur DC, Lawrence D, et al. Secondary cytogenetic changes in acute promyelocytic leukemia--prognostic importance in patients treated with chemotherapy alone and association with the intron 3 breakpoint of the PML gene: a Cancer and Leukemia Group B study. J Clin Oncol. 1997;15:1786–95. https://doi.org/10.1200/jco.1997.15.5.1786.
31. Hiorns LR, Swansbury GJ, Mehta J, et al. Additional chromosome abnormalities confer worse prognosis in acute promyelocytic leukaemia. Br J Haematol. 1997;96:314–21.
32. De Botton S, Chevret S, Sanz M, et al. Additional chromosomal abnormalities in patients with acute promyelocytic leukaemia (APL) do not confer poor prognosis: results of APL 93 trial. Br J Haematol. 2000;111:801–6.
33. Hernández JM, Martín G, Gutiérrez NC, et al. Additional cytogenetic changes do not influence the outcome of patients with newly diagnosed acute promyelocytic leukemia treated with an ATRA plus anthracyclin based protocol. A report of the Spanish group PETHEMA. Haematologica. 2001;86:807–13.
34. Cervera J, Montesinos P, Hernández-Rivas JM, et al. Additional chromosome abnormalities in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and chemotherapy. Haematologica. 2010;95:424–31. https://doi.org/10.3324/haematol.2009.013243.
35. Poiré X, Moser BK, Gallagher RE, et al. Arsenic trioxide in front-line therapy of acute promyelocytic leukemia (C9710): prognostic significance of FLT3 mutations and complex karyotype. Leuk Lymphoma. 2014;55:1523–32. https://doi.org/10.3109/10428194.2013.842985.

36. De Botton S, Dombret H, Sanz M, et al. Incidence, clinical features, and outcome of all trans-retinoic acid syndrome in 413 cases of newly diagnosed acute promyelocytic leukemia. The European APL Group. Blood. 1998;92:2712–8.
37. Jeddi R, Ghédira H, Mnif S, et al. High body mass index is an independent predictor of differentiation syndrome in patients with acute promyelocytic leukemia. Leuk Res. 2010;34:545–7.
38. Breccia M, Mazzarella L, Bagnardi V, et al. Increased BMI correlates with higher risk of disease relapse and differentiation syndrome in patients with acute promyelocytic leukemia treated with the AIDA protocols. Blood. 2012;119:49–54.
39. Leblebjian H, Deangelo DJ, Skirvin JA, et al. Predictive factors for all-trans retinoic acid-related differentiation syndrome in patients with acute promyelocytic leukemia. Leuk Res. 2013;37:747–51. https://doi.org/10.1016/j.leukres.2013.04.011.
40. Norsworthy KJ, Altman JK. Optimal treatment strategies for high-risk acute promyelocytic leukemia. Curr Opin Hematol. 2016;23:127–36. https://doi.org/10.1097/MOH.0000000000000215.
41. Abla O, Ribeiro RC, Testi AM, et al. Predictors of thrombo-hemorrhagic early death in children and adolescents with t(15;17) positive acute promyelocytic leukemia treated with ATRA and chemotherapy. Ann Hematol. 2017;96(9):1449–56. https://doi.org/10.1007/s00277-017-3042-6.
42. Mell LK, Jeong J-H. Pitfalls of using composite primary end points in the presence of competing risks. J Clin Oncol. 2010;28:4297–9. https://doi.org/10.1200/JCO.2010.30.2802.
43. Sanz MA, Lo-Coco F, Martín G, et al. Definition of relapse risk and role of nonanthracycline drugs for consolidation in patients with acute promyelocytic leukemia: a joint study of the PETHEMA and GIMEMA cooperative groups. Blood. 2000;96:1247–53.
44. Tallman MS, Kim HT, Montesinos P, et al. Does microgranular variant morphology of acute promyelocytic leukemia independently predict a less favorable outcome compared with classical M3 APL? A joint study of the North American Intergroup and the PETHEMA Group. Blood. 2010;116:5650–9. https://doi.org/10.1182/blood-2010-06-288613.
45. Noguera NI, Breccia M, Divona M, et al. Alterations of the FLT3 gene in acute promyelocytic leukemia: association with diagnostic characteristics and analysis of clinical outcome in patients treated with the Italian AIDA protocol. Leukemia. 2002;16:2185–9. https://doi.org/10.1038/sj.leu.2402723.
46. Au WY, Fung A, Chim CS, et al. FLT-3 aberrations in acute promyelocytic leukaemia: clinicopathological associations and prognostic impact. Br J Haematol. 2004;125:463–9. https://doi.org/10.1111/j.1365-2141.2004.04935.x.
47. Gale RE, Hills R, Pizzey AR, et al. Relationship between FLT3 mutation status, biologic characteristics, and response to targeted therapy in acute promyelocytic leukemia. Blood. 2005;106:3768–76. https://doi.org/10.1182/blood-2005-04-1746.
48. Chillón MC, Santamaría C, García-Sanz R, et al. Long FLT3 internal tandem duplications and reduced PML-RARα expression at diagnosis characterize a high-risk subgroup of acute promyelocytic leukemia patients. Haematologica. 2010;95:745–51. https://doi.org/10.3324/haematol.2009.015073.
49. Beitinjaneh A, Jang S, Roukoz H, Majhail NS. Prognostic significance of FLT3 internal tandem duplication and tyrosine kinase domain mutations in acute promyelocytic leukemia: a systematic review. Leuk Res. 2010;34:831–6. https://doi.org/10.1016/j.leukres.2010.01.001.
50. Hong S-D, Kim Y-K, Kim H-N, et al. Treatment outcome of all-trans retinoic acid/anthracycline combination chemotherapy and the prognostic impact of FLT3/ITD mutation in acute promyelocytic leukemia patients. Korean J Hematol. 2011;46:24–30. https://doi.org/10.5045/kjh.2011.46.1.24.
51. Schnittger S, Bacher U, Haferlach C, et al. Clinical impact of FLT3 mutation load in acute promyelocytic leukemia with t(15;17)/PML-RARA. Haematologica. 2011;96:1799–807. https://doi.org/10.3324/haematol.2011.049007.
52. Barragán E, Montesinos P, Camos M, et al. Prognostic value of FLT3 mutations in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and anthracycline monochemotherapy. Haematologica. 2011;96:1470–7. https://doi.org/10.3324/haematol.2011.044933.
53. Breccia M, Loglisci G, Loglisci MG, et al. FLT3-ITD confers poor prognosis in patients with acute promyelocytic leukemia treated with AIDA protocols: long-term follow-up analysis. Haematologica. 2013;98:e161–3. https://doi.org/10.3324/haematol.2013.095380.
54. Lucena-Araujo AR, Kim HT, Jacomo RH, et al. Internal tandem duplication of the FLT3 gene confers poor overall survival in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and anthracycline-based chemotherapy: an International Consortium on Acute Promyelocytic Leukemia study. Ann Hematol. 2014;93:2001–10. https://doi.org/10.1007/s00277-014-2142-9.
55. Cicconi L, Divona M, Ciardi C, et al. PML-RARα kinetics and impact of FLT3-ITD mutations in newly diagnosed acute promyelocytic leukaemia treated with ATRA and ATO or ATRA and chemotherapy. Leukemia. 2016;30:1987–92. https://doi.org/10.1038/leu.2016.122.
56. Shen Y, Fu Y-K, Zhu Y-M, et al. Mutations of epigenetic modifier genes as a poor prognostic factor in acute promyelocytic leukemia under treatment with all-trans retinoic acid and arsenic trioxide. EBioMedicine. 2015;2:563–71. https://doi.org/10.1016/j.ebiom.2015.04.006.
57. Nolte F, Hecht A, Reinwald M, et al. In acute promyelocytic leukemia (APL) low BAALC gene expression identifies a patient group with favorable overall survival and improved relapse free survival.

Leuk Res. 2013;37:378–82. https://doi.org/10.1016/j.leukres.2012.11.018.
58. Hecht A, Nowak D, Nowak V, et al. High expression of the Ets-related gene (ERG) is an independent prognostic marker for relapse-free survival in patients with acute promyelocytic leukemia. Ann Hematol. 2013;92:443–9. https://doi.org/10.1007/s00277-012-1648-2.
59. Hecht A, Nolte F, Nowak D, et al. Prognostic importance of expression of the Wilms' tumor 1 gene in newly diagnosed acute promyelocytic leukemia. Leuk Lymphoma. 2015;56:2289–95. https://doi.org/10.3109/10428194.2014.990011.
60. Hecht A, Nowak D, Nowak V, et al. A molecular risk score integrating BAALC, ERG and WT1 expression levels for risk stratification in acute promyelocytic leukemia. Leuk Res. 2015;39:1172–7. https://doi.org/10.1016/j.leukres.2015.08.010.
61. Lucena-Araujo AR, Kim HT, Jacomo RH, et al. Prognostic impact of KMT2E transcript levels on outcome of patients with acute promyelocytic leukaemia treated with all-trans retinoic acid and anthracycline-based chemotherapy: an International Consortium on Acute Promyelocytic Leukaemia study. Br J Haematol. 2014;166:540–9. https://doi.org/10.1111/bjh.12921.
62. Santamaría C, Chillón MC, García-Sanz R, et al. The relevance of preferentially expressed antigen of melanoma (PRAME) as a marker of disease activity and prognosis in acute promyelocytic leukemia. Haematologica. 2008;93:1797–805. https://doi.org/10.3324/haematol.13214.
63. Baljevic M, Dumitriu B, Lee J-W, et al. Telomere length recovery: a strong predictor of overall survival in acute promyelocytic leukemia. Acta Haematol. 2016;136:210–8. https://doi.org/10.1159/000448160.
64. Mandelli F, Diverio D, Avvisati G, et al. Molecular remission in PML/RAR alpha-positive acute promyelocytic leukemia by combined all-trans retinoic acid and idarubicin (AIDA) therapy. Gruppo Italiano-Malattie Ematologiche Maligne dell'Adulto and Associazione Italiana di Ematologia ed Oncologia Pediatrica Cooperative Groups. Blood. 1997;90:1014–21.
65. Sanz MA, Martín G, Rayon C, et al. A modified AIDA protocol with anthracycline-based consolidation results in high antileukemic efficacy and reduced toxicity in newly diagnosed PML/RARalpha-positive acute promyelocytic leukemia. PETHEMA group. Blood. 1999;94:3015–21.
66. Ferrara F, Morabito F, Martino B, et al. CD56 expression is an indicator of poor clinical outcome in patients with acute promyelocytic leukemia treated with simultaneous all-trans-retinoic acid and chemotherapy. J Clin Oncol. 2000;18:1295–300. https://doi.org/10.1200/JCO.2000.18.6.1295.
67. Ito S, Ishida Y, Oyake T, et al. Clinical and biological significance of CD56 antigen expression in acute promyelocytic leukemia. Leuk Lymphoma. 2004;45:1783–9. https://doi.org/10.1080/10428190410001683624.
68. de Botton S, Sanz MA, Chevret S, et al. Extramedullary relapse in acute promyelocytic leukemia treated with all-trans retinoic acid and chemotherapy. Leukemia. 2005;20:35–41. https://doi.org/10.1038/sj.leu.2404006.
69. Montesinos P, Díaz-Mediavilla J, Debén G, et al. Central nervous system involvement at first relapse in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and anthracycline monochemotherapy without intrathecal prophylaxis. Haematologica. 2009;94:1242–9. https://doi.org/10.3324/haematol.2009.007872.
70. Montesinos P, González JD, Gonzalez J, et al. Therapy-related myeloid neoplasms in patients with acute Promyelocytic leukemia treated with all-trans-retinoic acid and anthracycline-based chemotherapy. J Clin Oncol. 2010;28:3872–9. https://doi.org/10.1200/JCO.2010.29.2268.
71. Martínez-Cuadrón D, Montesinos P, Vellenga E, et al. Long-term outcome of elderly patients with newly diagnosed acute promyelocytic leukemia treated with ATRA plus anthracycline-based therapy. Leukemia accepted article preview 6 June 2017; doi: 10.1038/leu.2017.178.
72. Yanada M, Matsushita T, Asou N, et al. Severe hemorrhagic complications during remission induction therapy for acute promyelocytic leukemia: incidence, risk factors, and influence on outcome. Eur J Haematol. 2007;78:213–9. https://doi.org/10.1111/j.1600-0609.2006.00803.x.