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REVIEW ARTICLE

Prognostic factors in acute promyelocytic leukemia: strategies to define high-risk patients

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Abstract All trans retinoic acid (ATRA) has revolutionized the therapy of acute promyelocytic leukemia (APL). Treatment of this leukemia with ATRA in combination with chemotherapy has resulted in complete remission rates >90 % and long-term remission rates above 80 %. Furthermore, the combination of ATRA and arsenic trioxide (ATO) was shown to be safe and effective in frontline treatment and, for patients with low and intermediate risk disease, possibly superior to the standard ATRA and anthracycline-based regimen. However, in spite of this tremendous progress, APL still remains associated with a high incidence of early death due to the frequent occurrence of an abrupt bleeding diathesis. This hemorrhagic syndrome more frequently develops in high-risk APL patients, currently defined as those exhibiting $>10 \times 10^9$/L WBC at presentation. In addition to high WBC count, other molecular and immunophenotypic features have been associated with high-risk APL. Among them, the expression in APL blasts of the stem/progenitor cell antigen CD34, the neural adhesion molecule (CD56), and the T cell antigen CD2 help to identify a subset of patients at higher risk of relapse and often the expression of these markers is associated with high WBC count. At the molecular level, the short PML/RARA isoform and *FLT3*-internal tandem duplication (ITD) mutations have been associated with increased relapse risk. These observations indicate that extended immunophenotypic and molecular characterization of APL at diagnosis including evaluation of CD2, CD56, and CD34 antigens and of *FLT3* mutations may help to better design risk-adapted treatment in this disease.

Keywords Acute myeloid leukemia · Acute promyelocytic leukemia · Prognosis · Membrane markers

Introduction

Acute promyelocytic leukemia (APL) is a distinct subset of acute myeloid leukemia (AML), characterized by peculiar molecular, morphologic, biologic, and clinical features. These features include a unique genetic abnormality consisting of a chromosomal translocation which fuses the 3′ region of the retinoic acid receptor A (RARA) gene to the 5′ region of the promyelocytic gene (PML) resulting in the chimeric PML-RARA oncoprotein, and an exquisite sensitivity of APL blasts to retinoic acid which induces in vitro and in vivo terminal granulocytic maturation of APL leukemic cells [reviewed in 1]. Numerous studies have shown that PML-RARA is the master driver of APL [reviewed in 2]. In addition to several functional studies carried out in PML-RARA transgenic mice [reviewed in 2], two additional observations suggested the unique role of PML-RARA as the single genetic event initiating APL development. First, Vickers and coworkers showed that APL incidence is approximately constant with respect to age, a finding which is not observed in other malignancies and compatible with the hypothesis that there is only one rate limiting genetic event responsible for disease initiation [3]. The second evidence derives from whole

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genome sequencing studies showing that APL blasts display an average of only three mutations in coding regions, the only mutation recurrently associated with t(15;17) being mutations in the *fms*-like tyrosine kinase 3 receptor (*FLT3*) gene [4, 5].

PML-RARA behaves like an abnormal RARA and interferes with RARA signaling, thus blocking myeloid cell differentiation and stimulating self-renewal; this determines an oncogenic signaling responsible for the development of a leukemic process characterized by the accumulation of undifferentiated and dysplastic promyelocytes. In vitro studies have shown that ATRA reverts PML-RARA-mediated transcriptional repression inducing the conversion of the PML-RARA hybrid from a transcriptional repressor to a transcriptional activator through a molecular process of conformational change, which in turn determines the release of co-repressors and the recruitment of co-activators. These molecular events restore the normal process of RAR-dependent transcriptional activation and induce terminal granulocytic differentiation [reviewed in 2].

In 1988, it was first shown that treatment of APL patients with ATRA resulted in disease remission by triggering of terminal granulocytic differentiation of leukemic promyelocytes [6]. When used as single agent, however, ATRA allowed only a transient blast cell clearance, and complete remission was followed in all cases by leukemia relapse; the combination of ATRA with anthracycline-based chemotherapy resulted in a pronounced antileukemic effect, being curative in up to 70 % of APL patients.

More recently, arsenic trioxide (ATO) has been shown to be able to induce the degradation of the PML-RARA fusion protein through binding the PML moiety of this molecule and has displayed a remarkable synergy with ATRA [reviewed in 7]. ATO combined to ATRA has been shown to provide at least similar outcome results as compared to ATRA and chemotherapy in non high-risk APL patients, resulting in potential cure in >90 % of cases thereby suggesting that chemotherapy could be safely omitted in this patient category [8].

Nevertheless, APL still remains associated with a high incidence of early death, due to a typical bleeding diathesis related to a disseminated intravascular coagulation syndrome linked to the secretion of plasminogen activators and lysosomal enzymes by leukemic cells. This syndrome is particularly frequent in high-risk patients, currently defined as those with $>10 \times 10^9$/L WBC at presentation [9]. In addition to high WBC counts, other molecular and immunophenotypic features have been associated with high-risk APL. In this review article, we briefly discuss recent studies aiming at identifying prognostic factors in APL. Improved prognostic assessment, integrating genotypic and phenotypic markers may help the development of optimized treatment.

Cellular prognostic markers

CD56

Under normal conditions, CD56 is not expressed in cells pertaining to the myeloid cell lineage and, particularly, is not expressed during normal granulopoiesis. However, CD56 expression was reported on immature myeloid cells (promyelocytes and myelocytes) in regenerating bone marrow cells of patients undergoing allogeneic stem cell transplantation, thus suggesting that aberrant CD56 expression may be observed on immature granulopoietic cells under conditions of increased proliferation or of increased growth factor stimulation [10].

CD56 is unexpectedly expressed in approximately 10 % of APL cases [11]. The analysis of a very large cohort of APL patients ($n=651$) allowed to show a link between CD56 expression and various biologic features: WBC counts at diagnosis were higher among $CD56^+$ compared to $CD56^-$ APL patients; $CD56^+$ APLs more frequently displayed bcr3 isoform and expression of some other membrane antigens including CD34, CD2, CD7, CD15, and CD117 [11]. The expression of CD56 on this large group of APL patients treated with conventional ATRA plus idarubicin was shown to be an independent prognostic factor for relapse: in fact, the 5-year relapse rate was 22 % for $CD56^+$, compared to 10 % for $CD56^-$ cases [11]. Other recent studies indicated a lack of prognostic role for CD56 expression in APL patients. Ono and coworkers reported on 239 APL patients undergoing treatment based on ATRA and chemotherapy; CD56 expression, which was detected in 9.6 % of cases, did neither affect the complete remission rate nor overall survival; however, in APL patients with higher WBC counts, CD56 expression was an unfavorable prognostic factor for event-free survival [12]. A study on 114 APL patients undergoing treatment with ATRA and idarubicin in the context of the AIDA 0493 protocol showed that $CD56^+$ patients had a significantly reduced 5-year overall survival and a higher frequency of relapse compared to $CD56^-$ ones [13]. Importantly, in APL patients treated with ATO-based frontline therapy, CD56 was an independent prognostic factor for 3-year RFS, but not for OS [14].

Aberrant CD56 expression has been also frequently observed on myeloid blasts of AMLs characterized by the translocation (8;21)/AML1-ETO [15]. In these patients, CD56 expression was associated with poor prognosis and extramedullary disease [16]. The aberrant CD56 expression on the leukemic blasts of PML-$RARA^+$ or AML1-ETO^+ AMLs does not seem per se to represent a negative prognostic factor in AML. More likely, molecular events co-existing together with CD56 expression in APLs or in AML1-ETO^+ AMLs, such as c-kit mutations [17] or additional chromosomal abnormalities such as trisomy 4 [18], may explain the link between aberrant CD56 expression and unfavorable

prognosis. Alternatively, it has been proposed that aberrant CD56 expression reflects in APL malignant transformation of an earlier pluripotent progenitor, less sensitive to the currently used anti-leukemic drugs in this setting.

CD2

Initial studies on CD2 in APL showed that inappropriate expression of this antigen was associated with microgranular morphology and bcr3 PML-RARα isoform [19, 20]. More recent studies analyzed in more detail the biological properties of $CD2^+$ APLs and their prognostic profile in the context of standard therapy based on ATRA + anthracycline-based chemotherapy. In this context, Albano and coworkers explored CD2 and CD34 expression in a group of 136 newly diagnosed APLs, showing that about 24 % of cases displayed aberrant CD2 expression: the majority of these $CD2^+$ APLs co-expressed CD34, while a minority of them was $CD34^-$; about 50 % of $CD34^+$ APLs was shown to be positive for CD2 expression [21]. The $CD34^+CD2^+$ APLs showed a higher WBC count and did not express CD15, HLA-DR, and CD56 expression compared to $CD34^-CD2^-$ APLs [21]. Interestingly, the majority of microgranular M3v cases (80 %) reported in this study were within the $CD2^+$ group [20]. However, no significant differences were observed between these two groups of APLs in terms of either baseline clinical features or response to therapy [21].

More recently, Xu and coworkers have retrospectively analyzed 132 Chinese patients with APL and reported the biologic features and response to therapy of $CD2^+$ APLs, compared to $CD2^-$ APLs [22]. A value of 20 % of positive cells was used as the cut-off to distinguish $CD2^+$ APLs from $CD2^-$ APLs [22]. At the biologic level, only WBC count and CD34 positivity were different in the two subgroups, both being higher in $CD2^+$ APLs than in $CD2^-$ APLs [22]. At the clinical level, CD2 positivity was associated with an increased rate of early death and with a reduced 5-year overall survival [22]. A multivariate analysis performed including CD2, CD34, and CD56 indicated that CD2 was an independent risk factor for early death [22]. However, when WBC was considered along with CD2, CD34, and CD56, the results showed that only WBC count was an independent risk factor for early death and lower complete remission and 5-year overall survival rates [22].

CD34

Low or absent CD34 expression is considered a typical feature of the APL immunophenotypic profile, together with absent HLA-DR expression. However, a small proportion of APL patients express CD34 in their blasts at diagnosis. The latter has been associated with leukocytosis, hypogranular morphology, and/or the S-form of the PML-RARA transcript [23–25]. M3v displays a clearly higher percentage of promyelocytes positive for CD34 compared to the classical hypergranular form [26]. A detailed analysis of CD34 expression in 136 cases of APL showed a 25 % positivity for $CD34^+$; about 50 % of these $CD34^+$ APLs is positive for CD2 expression and predominantly express the bcr3 PML/RARA isoform; furthermore, 50 % of M3v APLs is $CD34^+$ [21].

Breccia and coworkers analyzed the prognostic impact of CD34 positivity in a group of 114 APL patients and observed that in 19 of these patients CD34 expression was associated with CD2 expression [27]. The CD34/CD2-positive APL subgroup displayed several differential properties compared to the CD34-negative APL population, including higher frequencies of M3v (27 % vs 7 %), bcr3 PML/RARA transcript type (72 % vs 32 %), higher incidence of differentiation syndrome (55 % vs 12 %), a higher rate of relapse (37 % vs 14 %), and lower overall survival (88 % vs 95 %) compared to CD34-negative patients [27]. In this study, isolated CD34 positivity alone without additional immunophenotypic makers allowed to identify a group of classic APL with an unfavorable clinical course.

In a recent study, Chendamarai and coworkers have analyzed the molecular and immunophenotypic features of APL patients relapsing after treatment with ATO alone [28]. At the immunophenotypic level, relapsing APLs were different from newly diagnosed APLs in terms of an increased expression of CD34 and a decreased expression of myeloid maturation markers such as CD13 and CD38 [28]. According to the observation that genes involved in the stem cell pathway are preferentially expressed in relapsing APLs, it was hypothesized the occurrence of a shift to a more immature phenotype and the expansion of the leukemia initiating compartment in relapsing APL patients [28].

WBC count

Several studies, most of which were conducted in the context of conventional ATRA and chemotherapy, have provided evidence that WBC count at diagnosis has important impact in clinical management of APL. Based on established consensus, WBC $\geq 10 \times 10^9$/L is considered to convey higher risk of both early death and relapse [29, 30]. In this context, Burnett and coworkers reported in 1999 that WBC count at diagnosis represents the only factor influencing APL outcome in patients receiving ATRA and chemotherapy: in this study, patients with WBC counts $\geq 10 \times 10^9$/L had an inferior CR, disease-free survival and overall survival rate and an increased incidence of early mortality and relapse compared to patients with WBC counts $< 10 \times 10^9$/L [31]. These findings were largely confirmed by a joint study of the Spanish Pethema and Italian Gimema cooperative groups. Accordingly, APL patients can be stratified into three relapse risk groups according to their WBC and platelet counts; the high risk group is

represented by APL patients with WBC counts $\geq 10 \times 10^9$/L [32]. Fenaux et al. further confirmed the prognostic role of WBC counts at diagnosis in APL, showing that even a modest increase in WBC count ($\geq 5 \times 10^9$/L) adversely impacted on the outcome of patients receiving standard ATRA + chemotherapy [33].

The introduction of ATO in the first line treatment regimen seemingly improved the therapeutic response of high-risk APL patients, but their response remained inferior to that observed in low-risk APL patients [34–36]. Recently, Daver and coworkers have retrospectively analyzed 242 consecutive APL patients, of whom 12 % had a WBC count $\geq 50 \times 10^9$/L [37]. Patients with hyperleukocytosis had inferior complete remission rates and higher 4-week mortality as compared to patients without hyperleucocytosis [37]. A proportion of these hyperleucocytic patients was treated with ATRA plus ATO therapy, while another with non-ATRA/ATO combinations; CR rate and 3-year overall survival were clearly better for the ATRA/ATO regimen [37].

A recent study in APL patients treated with ATO-based frontline therapy showed that WBC was an independent prognostic factor for OS, but not for RFS; the reduced OS was largely related to a markedly higher rate of early death observed among hyperleucocytic patients [14]. By analyzing a large number of APL patients treated with ATRA plus idarubicin in the context of two large clinical trials, Montesinos and coworkers found that a WBC greater than 5×10^9/L significantly correlates with an increased risk of developing severe differentiation syndrome [38].

Molecular prognostic markers

FLT3-ITD

It is well known that activating internal tandem duplication (ITD) mutations in the *Fms*-Like Tyrosine kinase 3 (*FLT3*) gene (*FLT3*-ITD) are associated with poor outcome in AMLs, but their prognostic significance in APLs has remained controversial. Mutations of the *FLT3* gene have been detected in 30–40 % of APLs: 20–30 % consist in ITDs occurring at the level of the juxtamembrane domain of the gene (*FLT3*-ITD); 8–12 % are activating point mutations occurring in the loop of the tyrosine kinase domain 2 (TDK2) of *FLT3*, mainly located at the level of the D835 amino acid residue [39, 40]. Both these mutations lead to the constitutive activation of *FLT3* tyrosine kinase. Studies in transgenic mice have shown a cooperation between PML-RARalpha and *FLT3*-ITD in the development of an APL-like disease in mice [41, 42]. These observations have generated the idea that APLs bearing *FLT3*-ITD could have a more aggressive leukemic phenotype associated with greater tendency to relapse.

The presence of *FLT3*-ITD in APL has been associated with various clinical and biological features including the following:

A) *Increased occurrence of thrombotic events*, as supported by an initial study of Breccia an coworkers on 135 APL patients [43] and recently confirmed by Mitrovic and coworkers on 63 APL patients [44]; the majority of these thrombotic events occurs during the induction phase of treatment.

B) *Increased white blood cell counts* (WBC), as initially described by Kiyoi and coworkers who reported increased WBC counts, as well as peripheral leukemia cell counts, and high LDH levels [39] and confirmed in numerous other studies [45, 46]. In the study carried out by Gale and coworkers on 203 APL patients, those with WBC counts of 10×10^9/L or greater had mutant *FLT3* [45]. Particularly pronounced was the effect of *FLT3* mutations on WBC counts in pediatric APL, with a median diagnostic WBC count of 23.4×10^9/L for those with *FLT3* mutations, compared to 3.6×10^9/L for those without FLT3 mutations [47].

C) *Immature cell phenotype*, as supported by various observations showing a higher CD34 expression in *FLT3*-ITD$^+$ APLs than in *FLT3*-ITD$^-$ APLs, a more immature morphology of leukemic promyelocytes, an aberrant CD2 expression (observed in the large majority of *FLT3*-ITD$^+$ APLs), and a higher frequency of microgranular variants (the large majority of M3v is observed among *FLT3*-ITD$^+$ APLs) [48].

D) *Preferential involvement of one of PML-RARα isoforms*: short/bcr3 isoform is much more frequent among *FLT3*-ITD$^+$ APLs (about 80 %) than among *FLT3*-ITD$^-$ APLs (about 20 %), the opposite being true for the long/bcr1 PML-RARα isoform [49].

The majority of clinical studies carried out on substantial number of APL patients treated with standard ATRA and chemotherapy have reported a negative prognostic impact of *FLT3*-ITD mutations, more related to an increased rate of relapses than to reduced rate of remissions after the induction therapy [reviewed in 50]. A study of an International Consortium on APL included 171 patients, 35 of whom were positive for *FLT3*-ITD mutation. After 38 months of median follow-up, *FLT3*-ITD mutant APLs had lower overall survival compared to *FLT3*-wild-type cases with no differences however in disease-free survival, complete remission rate, and cumulative incidence of relapse [51]. Another study attempted to define the variables within the *FLT3*-ITD group that could affect prognosis: (a) the *FLT3*-ITD/*FLT3*-wild-type ratio was an important prognostic parameter in that only patients with a high ratio and not those with a low ratio have a reduced probability of relapse-free survival; (b) the size of the ITD region

within the *FLT3* mutant molecule is another important prognostic determinant, with only APL patients with a long FLT3-ITD molecule exhibiting a reduced probability of relapse-free survival [52].

Interestingly, two recent studies carried out in patients receiving ATO-based frontline therapy failed to show a significant impact of *FLT3*-ITD as an independent marker on either RFS or OS [28, 53].

In addition to these biological and clinical associations, some studies have suggested a possible correlation between *FLT3*-ITD and the occurrence of early death in APL patients. In this respect, Gale and coworkers in a study of 203 adult and pediatric APL patients reported a significantly higher rate of deaths during the induction phase therapy in *FLT3*-ITD$^+$ APLs, compared to *FLT3*-ITD$^-$ APLs (19 % vs 9 %) [45]. Kutny and coworkers in a clinical study involving 104 pediatric APLs reported a markedly higher rate of early deaths among *FLT3*-ITD$^+$ APLs (30 %) compared to *FLT3*-wild type (3 %) [47].

Additional gene mutations

A recent study explored the possible impact of additional gene mutations on the outcome of APL patients undergoing treatment with ATRA + ATO. Interestingly, a greater number of high-risk APL patients carried additional mutations as compared to intermediate- and low-risk patients; more importantly, patients with mutations of the epigenetic modifier genes (DNMT3A, MLL, IDH1, IDH2, and TET2) displayed a significantly reduced OS and RFS, compared to patients lacking these mutations [54].

Wilms tumor 1 (WT1) has been found to be mutated in 11 % of APL patients; however, according to a recent study, WT1 mutations did not seem to impact on APL prognostic outcome [55, 56].

Additional chromosomal abnormalities

Additional chromosomal abnormalities (ACAs), in addition to the pathognomic t(15;17), are observed in about 28 % of APL patients and are mostly represented by trisomy 8 and abn(7q). Patients with ACAs more frequently had coagulopathy, lower platelet counts, and higher relapse risk scores than the other APL patients without ACAs; however, neither the ensemble of ACAs nor any specific ACA could be identified as independent risk factors for relapse [57]. A similar conclusion was reached in the context of the APL 93 trial showing that ACAs in patients with APL do not confer poor prognosis [58].

Genes abnormally expressed in APL

Various gene expression studies have shown that some genes differentially expressed in APLs may have a prognostic impact. Expression of the lymphoid enhancer-binding factor 1 (LEF1), a downstream effector of the Wnt/β-catenin signaling pathway, was very heterogeneous in primary APL cells: patients with low LEF1 expression had a poorer prognosis than those with high LEF1 expression [59]. High ERG expression was found to be an independent prognostic marker for relapse-free survival in patients with APL; furthermore, high ERG expression was significantly associated with inferior OS [60].

A recent study evaluated the prognostic impact of the lysine (K)-specific methyltransferase 2E (KMTE2) transcription levels on outcome of patients with APL treated with retinoic acid and anthracycline-based chemotherapy: particularly, low KMTE2 levels are associated in both univariate and multivariate analysis with a lower remission rate and overall survival [61]. These results are particularly relevant, given the biological function of KMTE2 a methyltransferase pertaining to the Trithorax family of histone-modifying proteins, which is involved in the control of terminal myeloid differentiation and facilitates retinoic-induced granulopoiesis in human promyelocytes [61].

TP73 isoforms

The TP73 gene transcript undergoes alternative splicing generating two transcriptionally active (Tap73) or inactive (ΔNp73) isoforms, exerting opposing effects on p53 target genes and induction of apoptosis. An imbalance of the ΔNp73 and Tap73 proteins ratio was found in many tumors to contribute to tumor development and resistance to treatment. In APl patients, a high ΔNp73/Tap73 expression ratio is an independent prognostic marker, being clearly associated with lower overall survival and higher cumulative incidence of relapse [62]. According to these findings, it was concluded that the ΔNp73/Tap73 ratio is an important determinant of clinical response in APL [62].

Genetic polymorphisms

Several gene polymorphisms play a key role in influencing the response of treatment of various cancers. In this context, particularly interesting were the results of a study carried out on 231 APL patients and showing that a functional variant in the core promoter of the CD95 death receptor gene (a common G > A polymorphism at position -1377) was associated with a worse prognosis in APL patients [63]. Particularly, APL patients with a WBC $\geq 3 \times 10^9/L^{-1}$ with a CD95-1377 genotype (GA or AA) have a significantly reduced overall survival and an increased death from infection than APL patients with a WBC $\geq 3 \times 10^9/L^{-1}$ with a CD95-1377 genotype (GG) [63]. The functional effect of the -1377 A variant is related to the destruction of

a binding site for the SP1 transcriptional regulator and the consequent reduced transcriptional activity of the CD95 promoter [63].

Early death

Currently, standard treatment of APL with ATRA and chemotherapy results in more than 90 % complete remission rates after induction treatment. However, early death, occurring either before treatment initiation or during induction, remains the main obstacle to final cure of the disease. In fact, nowadays, early death rather than resistant disease represents the major cause of treatment failure in APL. After the systematic introduction of ATRA in modern regimens, most early deaths have been recorded within the first 2–3 weeks. The main cause of early death in these patients is bleeding, often occurring at the intracranial level [64].

In this context, an important study by Park and coworkers published in 2011 and based on an epidemiological study carried out on a total of unselected 1400 APL patients, showed that the rate of early death remained high, despite the introduction of ATRA in the current therapy, with an overall early death rate of 17.3 %, only modestly changing over time [30]. This study indicated also that the early death rate observed in unselected APL patients was higher than commonly reported in patients entering into multicenter clinical trials [30].

Hemorrhagic events account for the majority (40–65 %) of early deaths, and several prognostic factors have been identified for such hemorrhagic deaths, including poor performance status, high WBC count, coagulopathy, CD2, and CD15 expression [reviewed in 64]. Furthermore, older age was found to be a prognostic factor of early death in all published APL series [30, 65–68].

The Spanish PETHEMA group analyzed causes and prognostic factors of induction failure in a large series of 732 patients treated with ATRA and chemotherapy. Again, hemorrhage was also in this study the most common cause of induction death (5 %), followed by infection (2.3 %) and differentiation syndrome (1.4 %). Multivariate analysis enabled to identify distinct characteristics associated with an increased risk of death caused by hemorrhage (abnormal creatinine level, increased peripheral blast counts, and presence of coagulopathy), infection (age > 60 years, male sex, and fever), and differentiation syndrome (Eastern cooperative oncology group [ECOG] score > 1 and low albumin levels), respectively [69].

Whether substitution of standard ATRA-chemotherapy regimens with arsenic-based treatments, at least in low- and intermediate-risk APL patients, will result in reduced early death rate is unknown and will likely be the subject of future investigation.

Conclusions

Risk assessment in APL management requires distinguishing prognostic factors associated with early death and increased probability of relapse. In addition, new treatment modalities including ATO may impact on the value of current prognostic factors which were mainly established in the context of ATRA and chemotherapy. The analysis of the available data indicates that, in spite the numerous prognostic biomarkers identified, the stratification of APL risk according to Sanz stratification based on WBC and platelet counts remains the most reliable and validated way to rapidly identify high-risk APL patients.

It is therefore important to rapidly identify these patients by comprehensive clinical, immunophenotypic, and molecular characterization in order to adopt optimized therapies. In this context, recent reports by Iland et al. [53], Daver et al. [37] and Burnett et al. [70] provided preliminary evidence that a therapeutic regimen based on frontline ATRA and ATO and an early cytoreduction with either idarubucin or gentuzumabozagamicin results in better outcome compared to frontline combinations that did not include ATO in high-risk APL patients. These findings need however to be confirmed in randomized clinical studies including a larger patient number and more mature follow-up.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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