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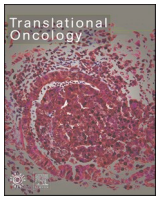

Original Research

Evolving of treatment paradigms and challenges in acute promyelocytic leukaemia: A real-world analysis of 1105 patients over the last three decades

Sun Teng-Fei [1], Abuduaini Diyaer [1], Zhu Hong-Ming, Chen Xin-Jie, Wang Wen-Fang, Zhao Yu-Bing, Lin Xiao-Jing [*], Cheng Wen-Yan [*], Shen Yang [*]

Shanghai Institute of Haematology, State Key Laboratory of Medical Genomics, National Research Centre for Translational Medicine at Shanghai, Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China

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ABSTRACT

Although acute promyelocytic leukaemia (APL) is a highly curable disease, challenges of early death (ED) and relapse still exist, and real-world data are scarce in the ATRA plus ATO era. A total of 1105 APL patients from 1990 to 2020 were enrolled and categorized into three treatment periods, namely ATRA, ATRA plus ATO, and risk-adapted therapy. The early death (ED) rate was 20.2%, 10.1%, and 7.0%, respectively, in three periods, while there was no significant decline in the 7-day death rate. Consistently, the overall survival (OS) and disease-free survival (DFS) of APL patients markedly improved over time. Despite the last two periods exhibiting similar DFS, the chemotherapy load was substantially lower in Period 3. Notably, leveraging older age and higher WBC count (especially $> 50 \times 10^9$/L), we could identify a small group of extremely high-risk patients who had a very high ED rate and poor prognosis, while those with *NRAS* mutations and higher WBC tended to relapse, both representing obstacles to curing all patients. In conclusion, the evolvement of treatment paradigms can reduce the ED rate, improve clinical outcomes, and spare patients the toxicity of chemotherapy. Special care and innovative agents are warranted for the particularly high-risk APL.

Introduction

Acute promyelocytic leukaemia (APL) is a unique subtype of acute myeloid leukaemia (AML), which is characterized by the balanced reciprocal translocation between chromosomes 15 and 17, generating a fusion gene, namely *PML-RARA*. As a representative paradigm of precision medicine, APL has become a successfully curable disease, owing to a series of paramount breakthroughs in the field of molecular-targeted and differentiation therapy over the past three decades. The emergence of all-trans retinoic acid (ATRA) remarkably revolutionized the treatment of the disease [1–3], and its combination with chemotherapy significantly improved the response rate and long-term outcomes [4–6]. Subsequently, the introduction of arsenic trioxide (ATO) further enhanced survival and guaranteed long-duration remissions in APL patients [7–9], which displayed a synergistic effect with ATRA in inducing the catabolism of the PML-RARA fusion protein [8]. In this context, we pioneered the combined use of ATRA and ATO and achieved a curative efficacy in more than 90% of newly diagnosed APL patients [10–15], which was then verified by a series of clinical trials conducted by international counterparts [12,16–18]. Since 2013, the reduction or elimination of chemotherapy according to the risk of patients with ATRA-ATO-based therapy has been tried [16,19,20]. Current risk-adapted therapy based on Sanz risk stratification represents the mainstay of APL management [21], which not only pursues a high cure rate, but also emphasizes the minimization of long-term toxicities and the improvement of patients' quality of life [16–20].

Nevertheless, as new treatment modalities emerge and evolve, our understanding of APL has long relied on clinical trials with strict inclusion and exclusion criteria under idealized conditions. Conversely, there is a paucity of population-based data to reflect the diagnosis, treatment, and survival of APL patients in the real world, which may contribute powerful evidence for the actual efficacy and safety of a treatment paradigm and facilitate more rational therapeutic decisions in the clinic. In this regard, it is necessary to obtain a global overview of the

* Corresponding authors.
E-mail addresses: me5537@126.com (L. Xiao-Jing), cheng_wenyan@126.com (C. Wen-Yan), yang_shen@sjtu.edu.cn (S. Yang).
[1] These authors contributed equally to this work.

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impact of these immense advances in treatment on this special patient population.

Early death (ED) remains the major obstacle to curing all APL patients, which is one of the most obvious differences between real-world practices and clinical trials. Compared with patients enrolled in clinical trials, unselected patients in the real world are predisposed to a significantly higher ED rate, ranging from 17.3% in the United States [22] to 29% in Sweden [23], and only a modest change could be observed in the ATRA plus chemotherapy era [22–26]. While this data was only 5–10% in various well-designed trials with the use of ATRA. Although ATO has been reported to dramatically reduce ED events [27,28], it remains unclear whether this improvement can be validated in a population-based APL cohort, especially in the era of ATRA-ATO treatment with the de-escalation or abrogation of cytotoxic chemotherapy.

Despite the Sanz score being widely used for identifying the risk of APL, additional genetic mutations as exemplified by *FLT3*-ITD or -TKD and *NRAS* are also considered to bear prognostic relevance, whereas the role of clinical and molecular parameters to predict relapse and survival remains ambiguous with the first-line use of ATRA plus ATO [29–33]. Moreover, prompt identification of patients with peculiar risk of ED is of importance for early therapeutic interventions in light of the emergence of novel drugs, which may contribute to the achievement of a curable goal in the vast majority of APL patients.

In this work, we conducted a hospital-based, real-world study by leveraging electronic and paper medical records collected from 1105 APL patients from the Shanghai Institute of Haematology (SIH), which spanned approximately 30 years. Through systematically comparing the three calendar periods which were classified by different treatment modalities, we intended to elucidate the overall tendency and actual benefits of the treatment evolvement from a real-world perspective. More importantly, by paying special attention to the ATRA-ATO-based era, we aimed to evaluate the amelioration of early deaths, address prognostic values of additional genetic mutations, and optimize the risk assignment of APL patients, which may provide a better framework for future rational management of the disease.

Materials and methods

Patient data

From January 1990 to December 2020, a total of 1105 patients with newly diagnosed APL at SIH were enrolled in this study, and they were divided into three calendar periods based on the treatment modality. Due to the limitations in ward size and difficulties in data collection at an early time, only cases with complete information in Period 1 (1990–2002) were incorporated. While for Period 2 (2003–2012) and Period 3 (2013–2020), all eligible hospitalized patients were consecutively included, representing the general patient population (Fig. 1). The diagnosis of APL was confirmed by the presence of t(15;17) in cytogenetic analysis or fluorescence *in situ* hybridization, or the positivity of *PML-RARA* fusion gene in reverse-transcriptase polymerase chain reaction (RT-PCR). In addition, *CBFβ-MYH11, RUNX1-RUNXT1, KMT2A*-PTD, and *KMT2A* rearrangements were screened by RT-PCR, and mutations in *NPM1, CEBPA, NRAS, WT1, FLT3*-ITD/TKD, *DNMT3A, IDH1/2, ASXL1* and *TET2* genes were detected by Sanger sequencing before 2019. The next-generation sequencing was conducted as routine since 2019 in our center. All genetic mutations were not selectively included, and only mutated genes were presented. APL patients were assigned to three risk groups per Sanz criteria. Patients with low and intermediate risk were collectively referred to as non-high risk (NHR).

This study was approved by the ethics committee of Ruijin Hospital. All patients had given informed consent for both treatment and cryopreservation of bone marrow (BM) and peripheral blood according to the Declaration of Helsinki.

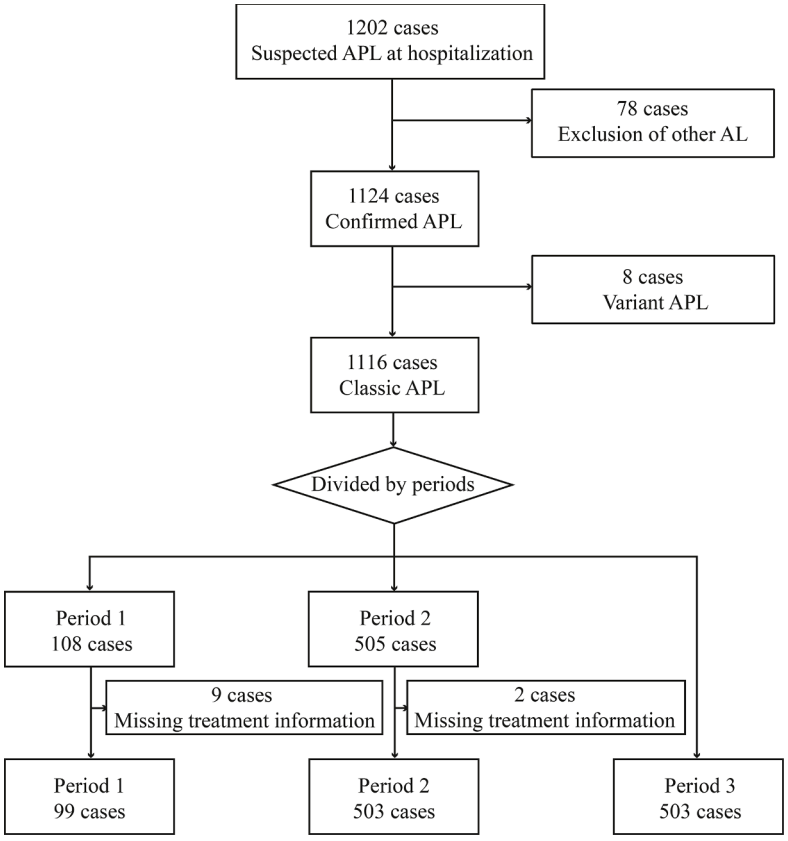


Fig. 1. Flowchart of inclusion and exclusion of all cases. A total of 78 cases without a definitive APL diagnosis, 8 cases with variant APL, and 11 cases in Period 1 and 2 with missing treatment information were excluded from this study.

Treatment

With a series of important findings in preclinical and clinical studies, treatment protocols of APL underwent corresponding modifications in each period, which could be briefly referred to as ATRA, ATRA plus ATO, and risk-adapted therapy, respectively.

In Period 1, ATRA and "3 + 7″ regimens (idarubicin, mitoxantrone, or daunorubicin; cytarabine) were administered as induction therapy, and consolidation therapy consisted of three cycles of ATRA and chemotherapy ("3 + 7″ regimens in the first two cycles; medium- to high-dose cytarabine in the third cycle).

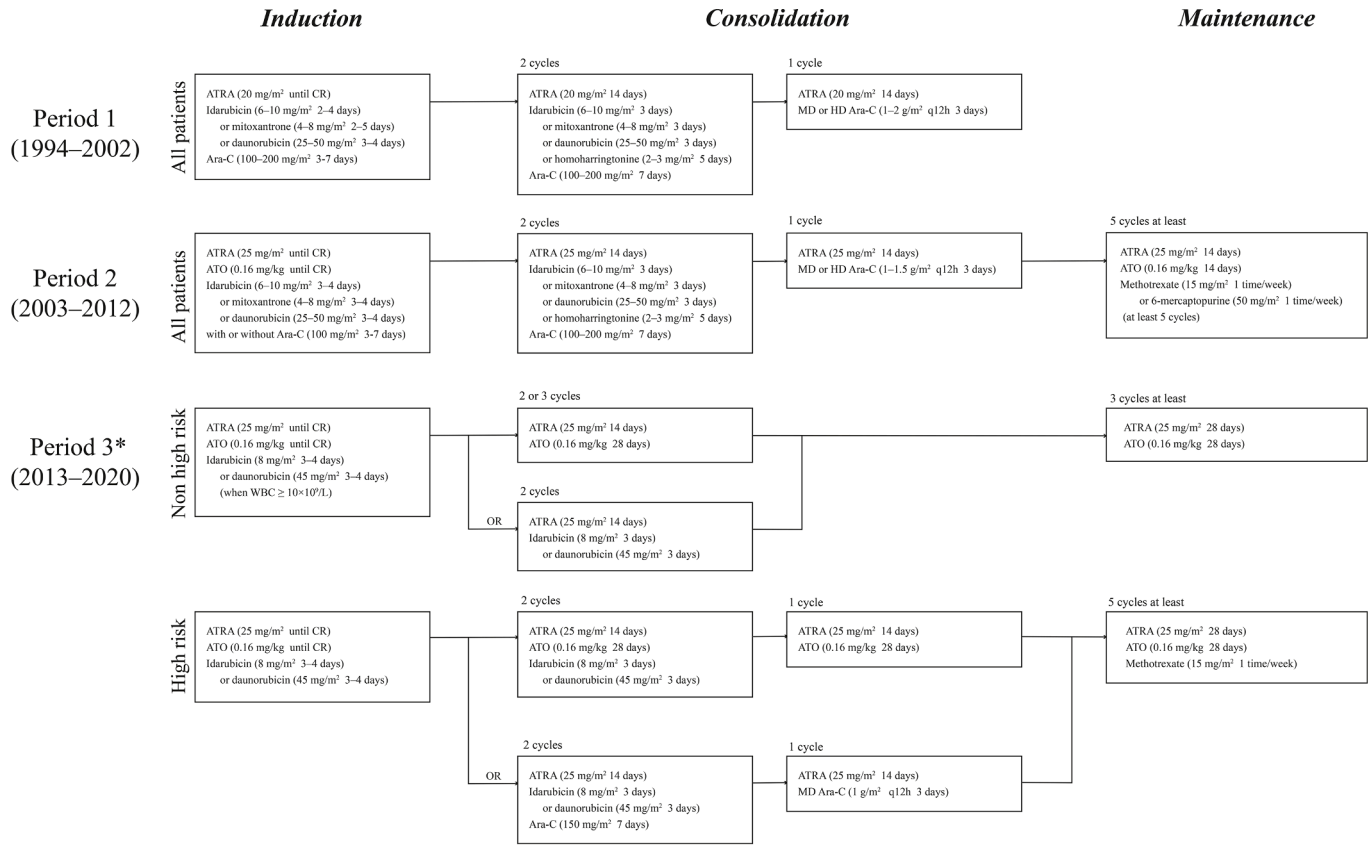
Due to the extraordinary therapeutic efficacy reported in the ATRA-ATO combination trial, since 2003, the beginning of Period 2, all patients at SIH received ATRA plus ATO and chemotherapy (idarubicin, mitoxantrone or daunorubicin, with or without cytarabine) as induction, and three cycles of ATRA plus chemotherapy ("3 + 7″ regimens in the first two cycles; medium- to high-dose cytarabine in the third cycle) as consolidation. For maintenance, in addition to ATRA plus ATO, methotrexate or 6-mercaptopurine was administered once a week for at least 5 cycles. It should be mentioned that in the first two periods, the dose and duration of chemotherapy use was flexibly adjusted according to the patient's condition.

Then, in Period 3, the risk-adapted treatment based on the Sanz risk score was implemented. For patients with non-high risk, ATRA plus ATO were given as induction therapy, with a small number of patients receiving additional chemotherapy (idarubicinor or daunorubicin) when the WBC count rised above 10×10^9/L. Similarly, most patients do not need extra chemotherapy as consolidation except for ATRA and ATO. For all high-risk patients, ATRA plus ATO and chemotherapy (idarubicin or daunorubicin) were used to induce remission. After attaining complete remission (CR), most high-risk APL patients received three cycles of ATRA plus ATO, with idarubicin or daunorubicin added in the first two cycles. For patients who were randomized to the non-ATO group in the APL2012 trial, the consolidation therapy comprised two courses of ATRA plus idarubicin or daunorubicin for non-high-risk patients, while three cycles of ATRA plus chemotherapy ("3 + 7″ regimens for the first two courses; medium-dose cytarabine for the third course) were delivered to high-risk patients. The maintenance therapy incorporated at least 3 cycles of ATRA plus ATO for patients with non-high risk, and at least 5 cycles of ATRA plus ATO and methotrexate for those with high risk. Detailed information regarding treatment schedule with dosage and duration in each period is provided in Fig. 2.

Statistical analysis

Early death was defined as death within 30 days of diagnosis. Overall survival was measured from the date of diagnosis to death from any cause, and patients who were still alive were censored for OS at the date of the last follow-up. Disease-free survival was calculated from the time of achieving CR to the date of relapse or death from any cause, whichever came first, and patients who were still alive in CR were censored for DFS at the last follow-up.

Categorical variables were compared by Fisher's exact test or chi-square test, and continuous variables by Wilcoxon rank sum test. Kaplan-Meier curves depicted the distribution of OS and DFS, and the log-rank test was used to compare the difference in survival. Multivariate analysis was conducted by using binary logistic regression for CR, and Cox proportional hazard model for OS and DFS, based on potential prognostic indicators in the univariate analysis. All statistical analyses were performed using the R (version 4.1.3) software package.



Abbreviation: ATRA, all-trans-retinoic acid; ATO, arsenic trioxide; Ara-C, cytarabine; CR, complete remission; MD, intermediate dose; HD, high dose.
*Treatment schedules in Periods 3 were referred to our previous clinical trial (Chen L, Zhu HM, Li Y, et al. Proc Natl Acad Sci U S A. 2021;118(6):e2020382118. doi:10.1073/pnas.2020382118).

Fig. 2. Treatment schedule in three periods.

Results

Characteristics of patients

Clinical characteristics of 1105 APL patients are summarized in Table 1, with 99, 503, and 503 patients, respectively, classified into the three calendar periods. The median age of all APL patients at diagnosis was 38 years (range, 14–80 years). There were no significant differences in age, gender, WBC count, and Sanz risk stratification among all periods. With regard to genetic mutations, the frequency of most mutated genes, as exemplified by *NRAS, WT1, FLT3*-ITD, *DNMT3A, IDH1,* and *ASXL1*, was not different among the three periods, with the exception of more *FLT3* TKD mutations (Period 1 vs 2 vs 3, 5.1 vs 5.0 vs 12.8%, $p < 0.001$) and less*TET2* mutations (Period 1 vs 2 vs 3, 2.4 vs 4.4 vs 0.5%, $p = 0.003$) in the third period, and a higher frequency *IDH2* mutations in Period 1 (Period 1 vs 2 vs 3, 2.2 vs 0.2 vs 0.3%, $p = 0.047$), respectively.

Early death

The occurrence of early death was recorded in 104 patients totally, with 20 (20.2%) patients in Period 1, 51 (10.1%) in Period 2, and 35 (7.0%) in Period 3, showing a declining tendency in ED rate over time (Period 1 vs 2, $p = 0.033$; Period 1 vs 3, $p = 0.001$), although there was no significant difference between the last two periods (Period 2 vs 3, $p = 0.123$) (Fig. 3A). Additionally, 49 patients succumbed to the disease within 7 days of diagnosis, and a similar trend of ED rate was observed in the three calendar periods (Period 1 vs 2 vs 3, 6.1 vs 5.0 vs 3.6%, all $p > 0.05$) (Fig. 3B). Notably, early deaths were more commonly seen in older patients (8.9% for $<$ 60 years, 17.6% for $\geq$ 60 years, $p < 0.001$) (Fig. 3C), and patients with higher WBC count (6.9% for $\leq 10 \times 10^9$/L, 13.2% for > 10 and $\leq 50 \times 10^9$/L, and 26.5% for $> 50 \times 10^9$/L, all $p < 0.05$) (Fig. 3D).

Survival and relapse

The median follow-up of patients was 60, 46, and 41 months, respectively, in the three periods. Patients in the first period carried the worst prognosis in terms of both OS (Period 1 vs 2, $p = 0.011$; Period 1 vs 3, $p < 0.001$) and DFS (Period 1 vs 2, $p = 0.004$; Period 1 vs 3, $p < 0.001$). Patients in Period 2 had a significantly poorer OS than those in Period 3 ($p = 0.016$), while the last two periods exhibited similar DFS ($p = 0.179$) (Fig. 4A and B). The 3-year OS rates were 78.4% (95% CI, 70.6–87.0%), 87.4% (95% CI, 85.0–90.8%) and 92.1% (95% CI, 89.8–94.5%), and 3-year DFS rates were 92.2% (95% CI, 86.3–98.4%), 93.9% (95% CI, 91.6–96.3%) and 95.3% (95% CI, 93.3–97.4%), respectively, for three periods.

Elderly APL patients (age > 60) demonstrated an inferior overall survival as compared to young patients (3-year OS rate, 89.6 vs 76.3%, $p < 0.001$), which could be attributed mainly to a higher ED rate in this population (Fig. 4C). Once CR was achieved, elderly patients experienced comparable disease-free survival as their younger counterparts (3-year DFS rate, 94.7 vs 89.3%, $p = 0.3$) (Fig. 4D). Higher WBC count exerted an adverse impact on clinical outcomes, as reflected in the Kaplan-Meier curves of three WBC groups which showed divergent probabilities of OS without overlapping (all $p < 0.05$) (Fig. 4E), and significantly different DFS between WBC count $\leq 10 \times 10^9$/L and the two high WBC groups (WBC count $\leq 10 \times 10^9$/L vs > 10 and $\leq 50 \times 10^9$/L, $p = 0.007$; WBC count $\leq 10 \times 10^9$/L vs $> 50 \times 10^9$/L, $p = 0.009$) (Fig. 4F). In addition, Sanz low-, intermediate- and high-risk patients demonstrated gradual deteriorating overall survival (all $p < 0.001$) (Fig. 4G), while those with low and intermediate risk had similar DFS ($p = 0.273$) (Fig. 4H).

Chemotherapy load

To clearly delineate the changes in chemotherapy use during different periods in a quantitative way, we artificially assigned every patient a chemotherapy load score, depending on specific chemotherapy regimens administered in addition to ATRA and/or ATO (0 score: no use of chemotherapy; 1 score: anthracycline-based regimens; 2 scores: anthracycline-based regimens plus Ara-C; 3 scores: medium or high dose of Ara-C). Individual scores of induction, consolidation, and total

Table 1
Clinical characteristics of APL patients.

Characteristics	Total	Period 1 (1994–2002)	Period 2 (2003–2012)	Period 3 (2013–2020)	P value	
Case, n (%)	1105 (100)	99 (9.0)	503 (45.5)	503 (45.5)	——	
Gender, n (%)						
Female	526 (47.6)	45 (45.6)	246 (48.9)	235 (46.7)	0.711	
Male	579 (52.4)	54 (54.4)	257 (51.1)	268 (53.3)		
Age (years), n (%)						
≤60	1020 (92.3)	93 (93.9)	461 (91.7)	466 (92.6)	0.685	
>60	85 (7.7)	6 (6.1)	42 (8.3)			37 (7.4)
WBC count ($\times 10^9$), n (%)						
≤10	802 (72.6)	77 (77.8)	374 (74.4)	351 (69.8)	0.184	
>10 & ≤50	220 (19.9)	16 (16.2)	99 (19.7)	105 (20.9)		
>50	83 (7.5)	6 (6.1)	30 (6.0)	47 (9.3)		
Risk stratification, n (%)						
Low risk	303 (27.4)	21 (21.2)	145 (28.8)	137 (27.2)		
Medium risk	499 (45.2)	56 (56.6)	229 (45.6)	0.079		214 (42.5)
High risk	303 (27.4)	22 (22.2)	129 (25.6)	152 (30.2)		
Mutation, n (%)						
NRAS	62 (5.9)	5 (5.3)	22 (4.6)	35 (7.3)	0.208	
WT1	136 (15.0)	9 (10.1)	72 (14.9)	55 (16.6)	0.31	
FLT3-ITD	141(13.0)	11(11.1)	55(11.2)	75 (15.2)	0.148	
FLT3-TKD	89 (8.2)	5 (5.1)	25 (5.0)	59 (11.9)	<0.001	
DMT3A	3 (0.3)	1 (1.1)	2 (0.4)	0 (0)	0.131	
IDH1	3 (0.3)	1 (1.1)	2 (0.4)	0 (0)	0.212	
IDH2	4 (0.4)	2 (2.2)	1 (0.2)	1 (0.3)	0.047	
ASXL	10 (1.1)	0 (0)	8 (1.7)	2 (0.5)	0.164	
TET2	25 (2.7)	2 (2.4)	21 (4.4)	2 (0.5)	0.003	
Outcome, n (%)						
Relapse	65 (5.8)	15 (15.2)	31 (6.2)	19 (3.8)	<0.001	
ED	106 (9.6)	20 (20.2)	51 (10.1)	35 (7.0)	0.002	

Abbreviation: WBC, white blood cell; ED: early death.

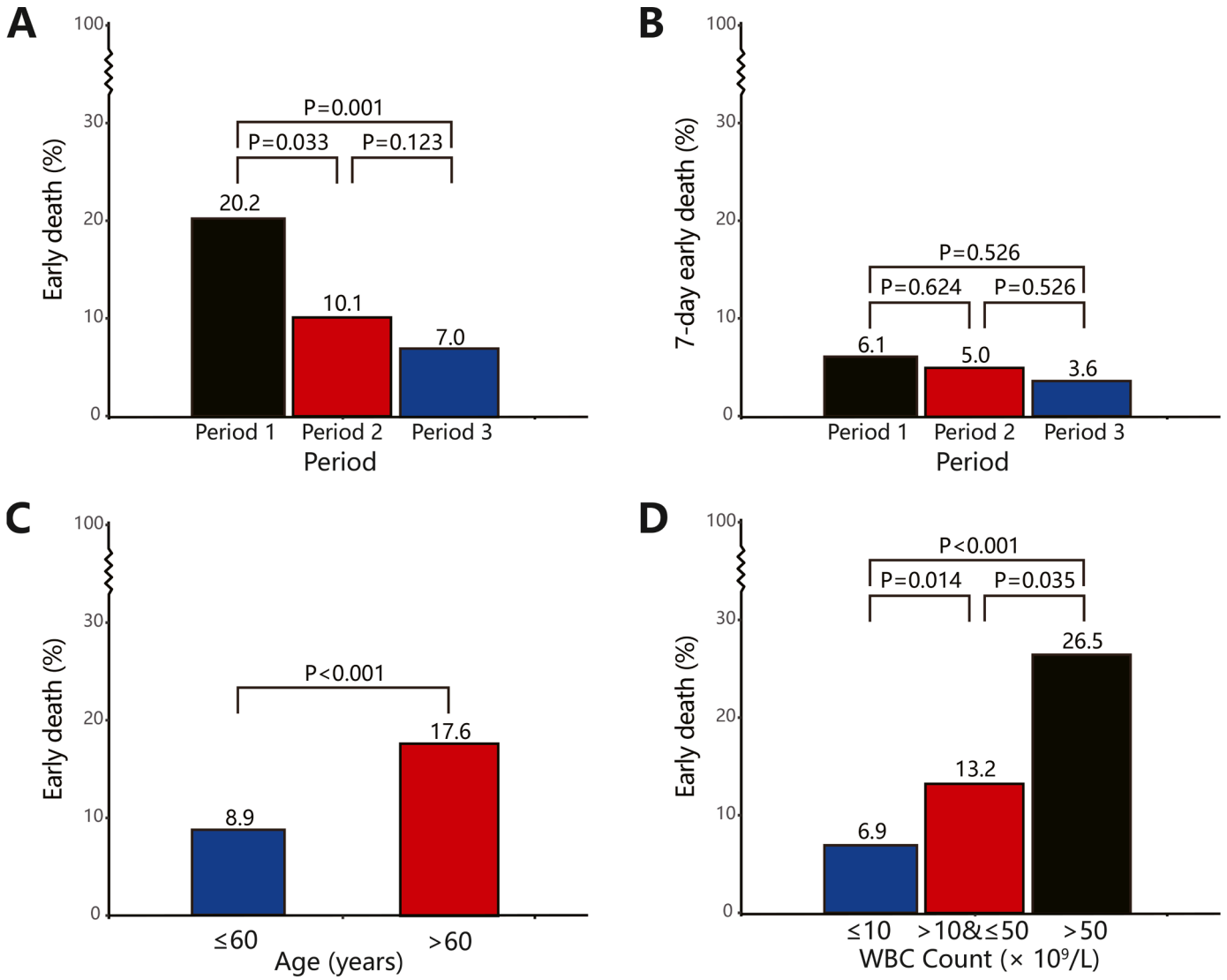


Fig. 3. Early death rates of APL patients. A, Early death rates of patients in three calendar periods. **B**, 7-day early death rates of patients in the three periods. **C**, Comparison of the early death rate between young (age < 60) and elderly (age ≥ 60) APL patients. **D**, Comparison of the early death rate in patients with WBC count ≤ 10 × 10^9/L, > 10 and ≤ 50 × 10^9/L, and > 50 × 10^9/L.

chemotherapy load were calculated for each patient and were arranged in the order of the date of diagnosis. It was apparent that the chemotherapy load decreased with time, which was most striking for the non-high-risk group in the third period (Fig. 5A).

We then statistically compared the average chemotherapy load over the three periods. For patients with non-high risk, a significant decrease in chemotherapy load could be observed between every two time periods, either for total, induction, or consolidation therapy (all $p < 0.001$) (Fig. 5B). While for high-risk patients, except for the total chemotherapy load ($p = 0.08$) and consolidation therapy load ($p = 0.281$) between the former two periods, there was a significant difference in each chemotherapy load score between all period pairs (all $p < 0.001$) (Fig. 5C).

Prognostic indicators in three periods

Given that clinical outcomes of APL patients varied in the three calendar periods, we sought to assess factors that were significantly associated with prognosis in each period (Table 2).

Prognostic indicators for OS in the multivariate analysis were identical in the last two periods, with age higher than 60 years (Period 2: HR = 3.190 95%CI, 1.536–6.627, $p = 0.002$; Period 3: HR = 3.229, 95%CI, 1.138–9.160, $p = 0.028$), WBC count > 10 and ≤ 50 × 10^9/L (Period 2: HR = 3.364, 95%CI, 1.819–6.221, $p < 0.001$; Period 3: HR = 5.426, 95% CI, 2.564–11.48, $p < 0.001$), and WBC count > 50 × 10^9/L (Period 2: HR = 7.923, 95%CI, 3.852–16.300, $p < 0.001$; Period 3: HR = 9.447, 95%CI, 3.998–22.320, $p < 0.001$) at diagnosis independently predicting an inferior OS.

In contrast, predictors for DFS differed in all three periods. In the first period, higher age (HR = 10.54, 95%CI, 2.559–43.41, $p = 0.001$) was independently associated with a shorter duration of DFS. In the second period, both WBC count > 10 and ≤ 50 × 10^9/L (HR = 2.660, 95%CI, 1.015–6.405 $p = 0.029$) and that > 50 × 10^9/L (HR = 3.992, 95%CI, 1.181–13.03, $p = 0.026$) conferred an adverse DFS after adjusting other prognostic parameters. While in the third period, it was important to note that only *NRAS* mutations (HR = 4.154, 95%CI, 1.350–12.78, $p = 0.013$) remained significant in the multivariate model, which could individually forecast a higher risk of relapse and death after achieving CR.

Construction of prediction model

Based on the results above, we next intended to develop a revised risk

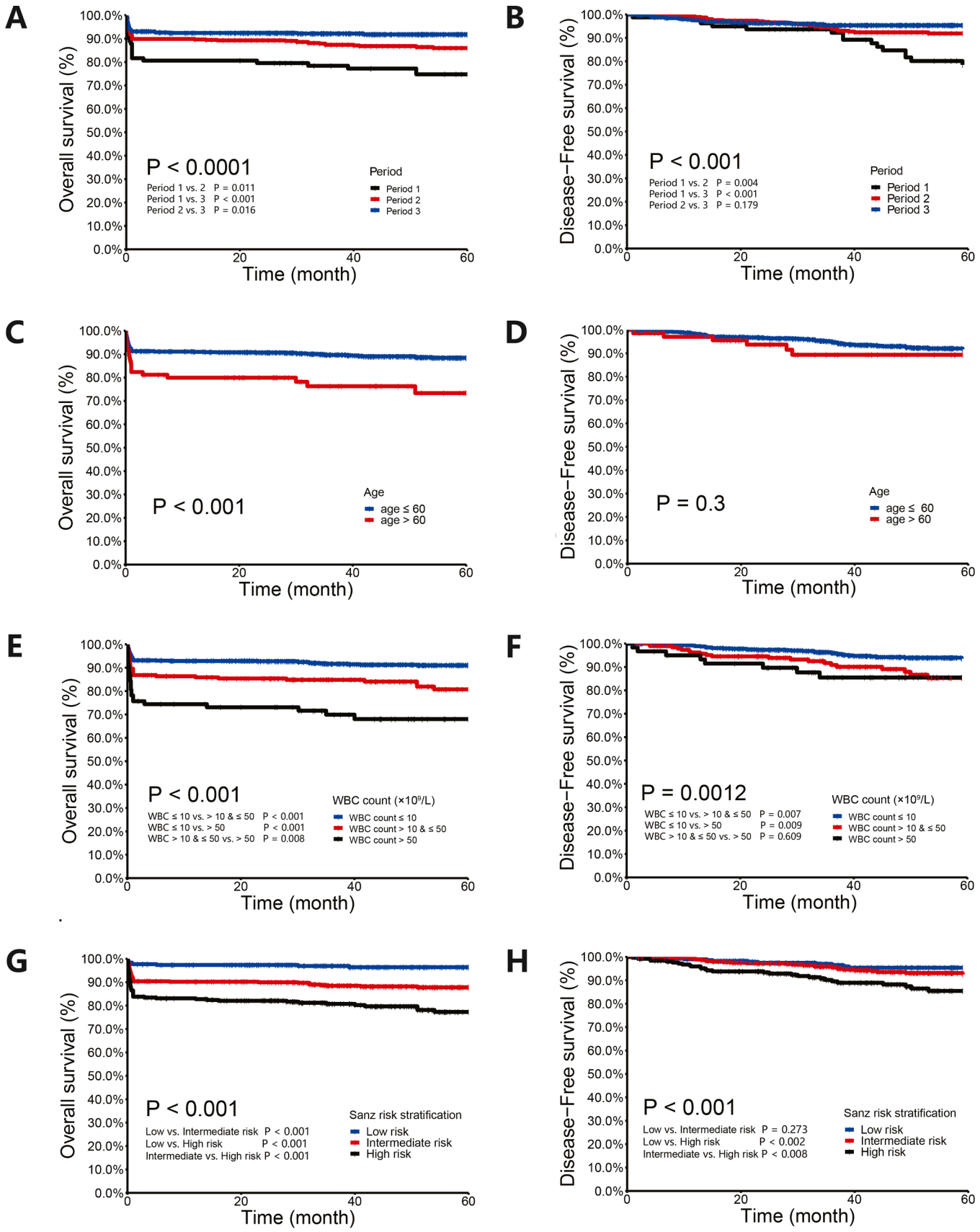


Fig. 4. Kaplan-Meier curves for the probability of overall survival and disease-free survival. Overall survival and disease-free survival of patients stratified by three periods (**A–B**), young (age < 60) and elderly (age ≥ 60) age group (**C–D**), WBC count ≤ 10×10^9/L, > 10 and ≤ 50×10^9/L, and > 50×10^9/L (**E–F**), and Sanz low-, intermediate- and high-risk groups (**G–H**).

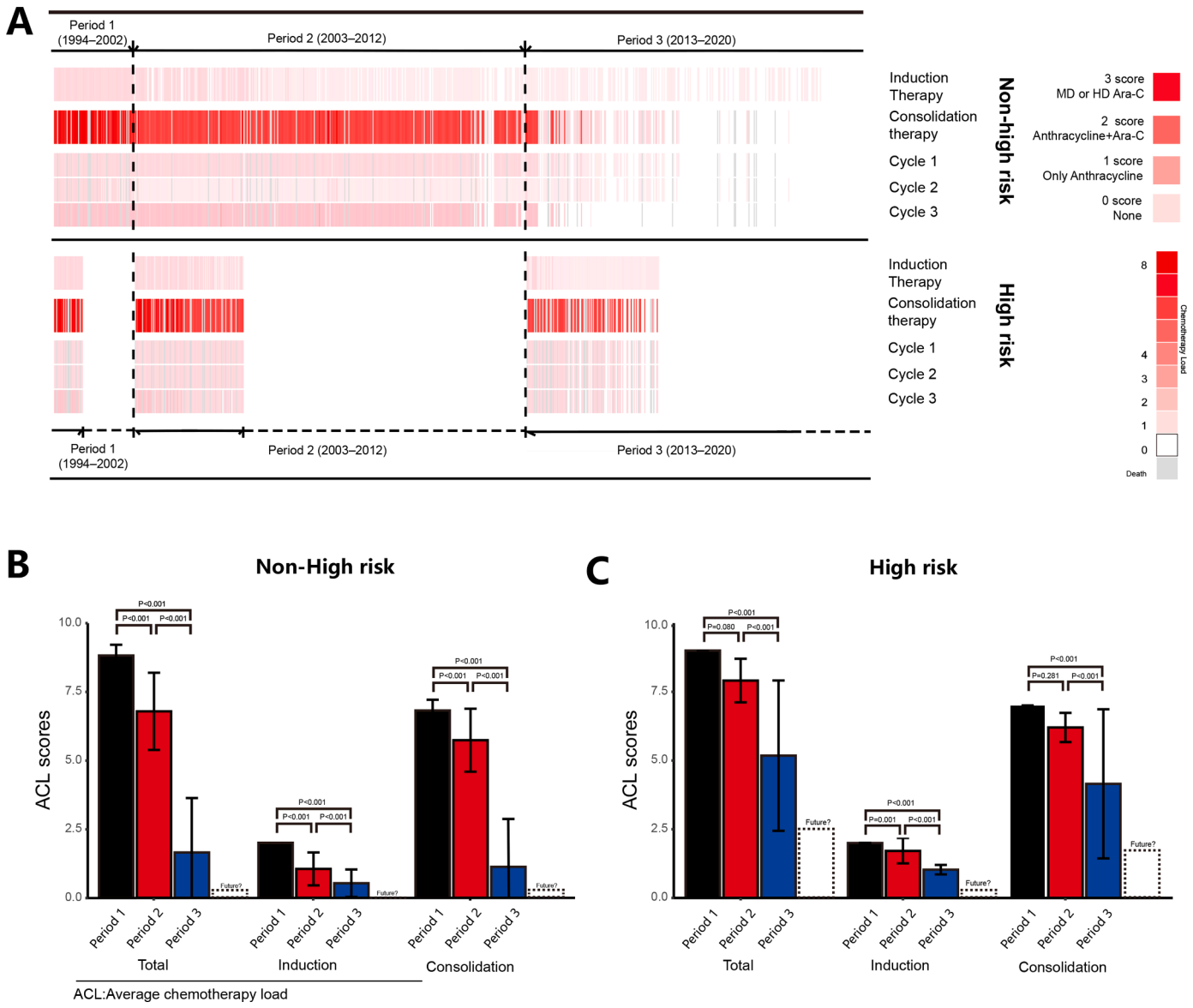


Fig. 5. Changes of chemotherapy load. A, Heatmap depicting chemotherapy load in APL patients stratified by three periods and Sanz risk score. Each column represents a patient, and the shade of color denotes chemotherapy load. All patients are arranged in the order of the date of diagnosis. **B–C**, Comparisons of average chemotherapy load, including total, induction and consolidation therapy load among the three periods, in patients with Sanz non-high risk (**B**) and high risk (**C**).

stratification system for OS and DFS by incorporating independent prognostic factors in the ATRA plus ATO era, which might enrich the widely used Sanz risk score and be more suitable for the current treatment modality. Hence, 1006 patients in the last two periods were combined and randomly separated into the training set ($n = 664$) and the validation set ($n = 342$) in a 2:1 ratio. Clinical characteristics of both sets are provided in Supplementary Table 1. There were no significant differences in clinical parameters and prognoses between the two cohorts.

Univariate and multivariate Cox analyses for both OS and DFS in the training set are provided (Fig. 6A). Multivariate modeling was conducted through the backward selection procedure, and two prognostic factors including age and WBC count were screened out and incorporated into the revised model. Each variable in the model was assigned a score, which was calculated by the β coefficient of the factor in the multivariate analysis that was divided by 0.8, multiplied by 2, and rounded off to the nearest integer. The revised risk score for OS was formulated as follows: high WBC count (> 10 and $\leq 50 \times 10^9$/L) *2 + very-high WBC count ($> 50 \times 10^9$/L) *3 + higher age (≥ 60 years) *3 (Fig. 6B). In the training set, the C-index was 0.659 (95%CI, 0.598–0.721), and patients could be separated into three risk groups, namely, the revised non-high risk (rNHR, $n = 433$, score = 0), the revised high risk (rHR, $n = 174$, score = 2), and the revised very high risk (rVHR, $n = 57$, score = 3–5) group (Fig. 6C). Overall, 42 patients with Sanz NHR were reclassified into the rHR group, who bore a significantly inferior OS ($P < 0.001$) than those who remained in the Sanz NHR group. Moreover, 57 patients with Sanz HR were reassigned into the rVHR group, showing a poorer prognosis than those in the Sanz HR group ($P < 0.001$) (Fig. 6D). Kaplan-Meier curves of three revised risk groups demonstrated statistically significant differences for probabilities of OS in both cohorts. In contrast to the Sanz risk score, our revised model could apparently distinguish a subset of APL patients with an extremely dismal prognosis (Fig. 6E). The prognosis of patients in the rVHR group was more adverse than those with rNHR and rHR in both training (both $P < 0.001$) and validation set (both $P < 0.001$).

Similar procedure was performed to construct a revised prediction model for DFS. *NRAS* mutations and higher WBC count were independent predictors in multivariate analysis. The final revised risk score for

Table 2
Logistic and cox analysis of three periods, respectively.

Variable		Period 1 (1994–2002)		Period 2 (2003–2012)		Period 3 (2013–2020)	
		HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
OS	**Univariate cox analysis**						
	Male	0.410 (0.431–2.147)	0.924	1.004 (0.619–1.626)	0.988	1.563 (0.615–3.970)	0.348
	Age (≥60)	0.618 (0.650–7.322)	0.207	2.598 (1.325–5.091)	0.005	3.166 (1.121–8.939)	0.03
	WBC count ($\times 10^9$/L)						
	≤10	1 [Reference]		1 [Reference]		1 [Reference]	
	>10 & ≤50	2.040 (0.791–5.263)	0.14	2.489 (1.428–4.338)	<0.001	4.018 (1.915–8.431)	<0.001
	>50	2.994 (0.863–10.39)	0.084	5.762 (3.030–10.96)	<0.001	6.531 (2.826–15.10)	<0.002
	FLT3-ITD mutation	1.496 (0.511–4.378)	0.462	0.832 (0.359–1.928)	0.668	0.629 (0.193–2.047)	0.441
	FLT3-TKD mutation	3.344 (0.993–11.26)	0.051	0.912 (0.286–2.905)	0.876	0.246 (0.059–1.024)	0.054
	NRAS mutation	1.694 (0.397–7.228)	0.477	1.037 (0.325–3.308)	0.951	2.611 (1.059–1.024)	0.031
	WT1 mutation	0.949 (0.219–4.110)	0.633	0.378 (0.389–1.711)	0.59	1.657 (0.782–3.511)	0.188
	Multivariate cox analysis						
	Male	————		————		————	
	Age (≥60)	————		3.190 (1.536–6.627)	0.002	3.229 (1.138–9.160)	0.028
	WBC count ($\times 10^9$/L)						
	≤10	————		1 [Reference]		1 [Reference]	
	>10 & ≤50	————		3.364 (1.819–6.221)	<0.001	5.426 (2.564–11.48)	<0.001
	>50	————		7.923 (3.852–16.30)	<0.001	9.447 (3.998–22.32)	<0.001
	FLT3-ITD mutation	————		————		————	
	FLT3-TKD mutation	————		————		————	
	NRAS mutation	————		————		————	
	WT1 mutation	————		————		————	
DFS	**Univariate cox analysis**						
	Male	0.519 (0.184–1.461)	0.214	1.294 (0.634–2.641)	0.479	1.563 (0.615–3.970)	0.361
	Age (≥60)	6.317 (1.769–22.55)	0.005	1.039 (0.248–4.355)	0.958	0.875 (0.117–6.564)	0.896
	WBC count ($\times 10^9$/L)						
	≤10	1 [Reference]		1 [Reference]		1 [Reference]	
	>10 & ≤50	1.553 (0.433–5.572)	0.665	2.659 (1.217–5.807)	0.014	2.802 (1.043–7.525)	0.041
	>50	2.041 (0.473–9.286)	0.495	4.296 (1.445–12.77)	0.009	2.880 (0.780–10.64)	0.113
	FLT3-ITD mutation	2.663 (0.847–8.377)	0.094	1.683 (0.644–4.398)	0.288	1.088 (0.317–3.734)	0.894
	FLT3-TKD mutation	3.344 (0.000–Inf)	0.051	2.213 (0.672–7.284)	0.191	0.360 (0.048–2.695)	0.32
	NRAS mutation	4.172 (0.939–18.53)	0.477	1.400 (0.333–5.877)	0.646	4.426 (1.442–13.58)	0.009
	WT1 mutation	1.443 (0.320–6.515)	0.633	0.370 (0.088–1.549)	0.173	0.339 (0.052–3.053)	0.377
	Multivariate cox analysis						
	Male	————		————		————	
	Age (≥60)	10.54 (2.559–43.41)	0.001	————		————	
	WBC count ($\times 10^9$/L)						
	≤10	————		1 [Reference]		————	
	>10 & ≤50	————		2.660 (1.105–6.405)	0.029	————	
	>50	————		3.992 (1.181–13.03)	0.026	————	
	FLT3-ITD mutation	————		————		————	
	FLT3-TKD mutation	————		————		————	
	NRAS mutation	————		————		4.154 (1.350–12.78)	0.013
	WT1 mutation	————		————		————	

Abbreviation: CR: complete remission; OS: overall survival; DFS: disease–free survival; OR: odds ratio; HR: hazard ratio; CI: confidence interval; WBC, white blood cell.

DFS was formulated by: high WBC count (> 10 and ≤ 50 $\times 10^9$/L) *1 + higher age (≥ 60 years) *2. The C-index was 0.707 (95%CI, 0.597–0.818) (Fig. 6F and G). A total of 24 patients with Sanz NHR were reclassified into rHR, displaying the same probability of DFS as Sanz HR (Fig. 6H). The revised model distinguished APL patients with relatively high and low risk of relapse and death after achieving CR in training ($P = 0.007$ and $P = 0.014$, respectively) and validation cohort ($P = 0.024$ and $P = 0.009$, respectively) (Fig. 6I).

Discussion

In the past few decades, the landscape of treatment in APL has undergone a tremendous paradigm shift. It is now generally accepted that APL is a curable disease, however, there still exist intractable issues, such as ED and relapse, which have not been addressed properly so far. Moreover, in contrast to clinical trials based on highly selected APL patients, population-based information reflecting realistic patterns of the disease is limited, especially in the era of ATRA-ATO-based stratified treatment. In this study, we collected complete diagnostic, treatment-related and follow-up data from a hospital-based clinical cohort comprising 1105 newly diagnosed APL patients, which was highly representative of the general patient population in the real world. As compared with other population-based studies, an evident strength of our study lies in the comprehensive and accurate clinical, molecular and survival data derived from medical records.

In the early 2000s, a pilot study was conducted at SIH, which showed that the combination of ATRA and ATO achieved superior therapeutic efficacy to ATRA or ATO alone [12]. Consequently, all primary APL patients had been treated with this combination strategy in addition to chemotherapy since 2003. In December 2012, we launched the APL2012 trial [20], and since then the ATRA-ATO-based risk-adapted treatment has become the cornerstone of APL management in our center. In this study, the entire cohort was separated into three calendar periods, corresponding to different treatment modalities, namely, ATRA, ATRA plus ATO, and risk-adapted therapy, that spanned over 30 years, a time period long enough to mirror these successive therapeutic advances over time.

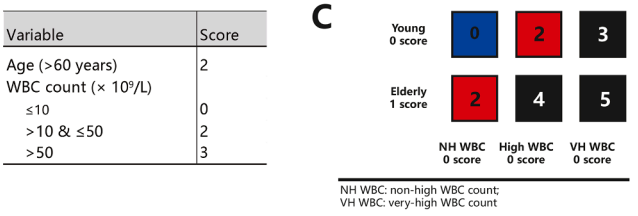
With the evolvement of treatment, the incidence of early death in APL patients declined over time. In the ATRA plus chemotherapy period, the ED rate was 20.2% in our study, which was in concordance with data reported in most population-based studies ranging from 14.6% to 29% in the same phase [22–26]. However, real-world data concerning the early death of APL in the ATRA plus ATO era are scarce. Of note, we observed a significantly lower ED rate of 10.1% in the

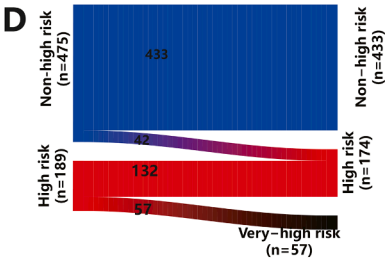
A

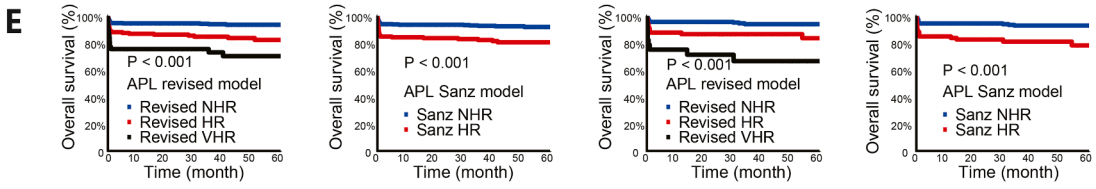
Variable	OS HR (95% CI)	OS P value	DFS HR (95% CI)	DFS P value
Univariate Cox analysis				
Male	1.049 (0.658–1.671)	0.841	1.807 (0.894–3.651)	0.099
Age (>60 years)	2.333 (1.227–4.438)	0.01	1.389 (0.425–4.544)	0.587
WBC count (×10^9)				
≤10	1 [Reference]		1 [Reference]	
>10 & ≤50	2.003 (1.159–3.460)	0.013	2.566 (1.236–5.328)	0.011
>50	4.354 (2.383–7.955)	<0.001	2.532 (0.857–7.483)	0.093
FLT3-ITD mutation	1.009 (0.162–1.636)	0.98	1.755 (0.764–4.030)	0.185
FLT3-TKD mutation	0.515 (0.162–1.636)	0.126	0.751 (0.180–3.133)	0.694
NRAS mutation	1.532 (0.661–3.547)	0.263	3.142 (1.206–8.184)	0.019
WT1 mutation	1.028 (0.503–2.101)	0.322	0.378 (0.088–1.545)	0.172
Multivariate Cox analysis				
Age (>60 years)	2.463 (1.289–4.706)	<0.001	———	
WBC count (×10^9)				
≤10	1 [Reference]		1 [Reference]	
>10 & ≤50	2.124 (1.226–3.680)	<0.001	2.242 (1.026–4.899)	0.043
>50	4.336 (2.374–7.921)	<0.001	———	
NRAS mutation	———		2.846 (1.075–7.512)	0.035

B

Variable	Score
Age (>60 years)	2
WBC count (× 10^9/L)	
≤10	0
>10 & ≤50	2
>50	3

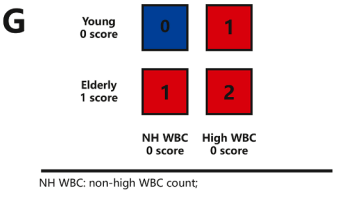


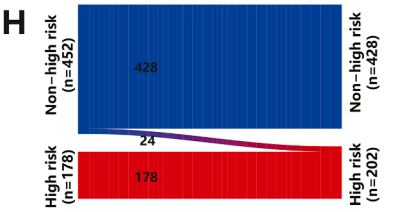




F

Variable	Score
NRAS Mutation (+)	1
WBC count (× 10^9/L)	
<10	0
>10 & ≤50	1





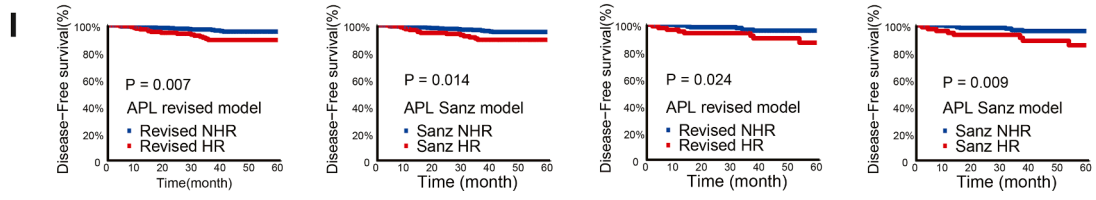


Fig. 6. Construction of revised prediction model. A, Univariate and multivariate Cox regression analysis of OS and DFS. **B**, Assignment of risk score to each variable predicting OS. **C**, Calculation process of cumulative risk score in the revised model for OS. Each cell of the chart represents the estimated risk of a patient, which is coloured according to the following risk groups: 0, 1–2 and 3–5. **D**, Sankey plot for reclassification from Sanz risk to the revised risk model for OS. **E**, Kaplan-Meier curves of OS displaying the revised risk groups and Sanz risk groups in the training and validation cohort, respectively. P value is calculated using the log-rank test. **F**, Assignment of risk score to each variable predicting DFS. **G**, Calculation process of cumulative risk score in the revised model for DFS. Each cell of the chart is the estimated risk of a patient, and is coloured by risk groups: 0 and 1–2. **H**, Sankey plot for reclassification from Sanz risk to the revised risk model for DFS. **I**, Kaplan-Meier estimates of DFS according to the revised risk groups and Sanz risks in the training cohort and validation cohort, respectively. P value is calculated using the log-rank test.

ATRA-ATO-chemotherapy period, which could be further reduced to 7.0% in the period of ATRA-ATO-based risk-stratified therapy. We speculate that the improvement in early mortality may be attributed to the following three aspects. Firstly, with the accumulation of knowledge and experiences, APL has gradually been recognized as a medical emergency, enabling prompt initiation of ATRA and better supportive care once the diagnosis of APL is suspected, leading to a significant decline in ED from the Period 1 to the latter two periods. Secondly, the introduction of ATO may also play an important role, as reported in clinical trials and a recent population-based study that ATO dramatically reduced the ED rate of APL [27,28,34]. Moreover, the administration of low-intensity or no chemotherapy during induction therapy may contribute to the decreased cytotoxic treatment-related mortality, which leads to an improvement of OS in Period 3 over Period 2, although similar ATRA-ATO-based treatment in both periods. Intracranial hemorrhage, differentiation syndrome (DS), and infections are among the most common causes of ED. Albeit the encouraging progress, there was no improvement in the 7-day mortality rate, suggesting that the ultra-early death remains a treatment bottleneck. In contrast, early mortality exceeding 7 days experienced an apparent decline in the last two periods. It is conceivable that the introduction of ATRA has largely reduced deaths within 7 days mainly due to intracranial hemorrhage, while the increased experiences of using ATO, steroids, and reduced chemotherapy help to decrease the risk of ED in the latter phase caused by DS and infections, but are incapable of further correcting coagulopathy on the basis of ATRA. Moreover, the enhanced supportive care may lead to a reduced risk of early death throughout the induction period.

Coinciding with the decline in the early death rate and fewer relapses owing to the introduction of ATO, both OS and DFS of APL patients has dramatically improved during the past decades. Furthermore, using the risk-adapted strategy could further achieve optimal treatment outcomes in terms of OS by reducing chemotherapy-related toxicities and early deaths. It is particularly noted that, with the wide adoption of ATRA and ATO, the decreased dose of cytotoxic chemotherapy could be observed over time, which was most pronounced in non-high-risk patients. As for the majority of high-risk APL, the anthracycline-based chemotherapy was indispensable, while cytarabine could be replaced, which was in line with the chemotherapy-deescalating strategy reported in the APL2012 trial. Collectively, these results demonstrated that the evolvement of treatment paradigms in APL has not only prolonged the survival time, but also spared patients the toxicity of intense chemotherapy.

However, with the introduction of ATRA-ATO into front-line treatment, prognostic indicators of APL have undergone a handful of changes as reflected in this study. In parallel, the efficacy of Sanz risk stratification in distinguishing different clinical outcomes has been mitigated, as exemplified by the similar DFS of patients with low to intermediate risk. Hence, risk factors related to relapse and long-term survival of APL may be reconsidered in this setting. Through combining the two ATRA-ATO-based periods, older age and higher WBC count, especially for those with a WBC count $> 50 \times 10^9$/L were proved to be independent adverse factors of OS, by which we constructed a revised risk scoring model for the prediction of OS. Apart from standard-risk and high-risk patients, we could identify a small group of extremely high-risk APL patients, who deserve special supportive care, especially in the induction phase when deaths are more commonly seen. A higher WBC count portends a great potential for hemorrhage-related mortality, especially for those with extreme hyperleukocytosis. Consequently, it is of paramount importance to immediately initiate the differentiation therapy, ameliorate the coagulopathy and avoid intracranial hemorrhage in treating these patients. While for elderly patients, both early bleeding risk, and DS- and infection-related deaths in the later stage are equally noteworthy. Hence, whole-course monitoring and aggressive supportive care should be provided for those above 60 years. Early interventions such as dexamethasone, targeted agents, and novel investigational drugs, as exemplified by ruxolitinib and tocilizumab are warranted. Notably, the JAK-STAT pathway inhibitor ruxolitinib may prevent or treat DS by reducing the production of cytokines, and a clinical trial is currently underway (NCT04446806). We anticipate that with these effective approaches, more early deaths can be preventable, and it may be possible to cure all APL patients in near future. Moreover, the presence of higher WBC count and *NRAS* mutations at diagnosis showed a propensity to relapse, and a revised prediction model for DFS was therefore developed, which could clearly discriminate patients with a higher risk of disease recurrence. In this regard, it is necessary to develop innovative approaches to eliminate relapse in patients with *NRAS* mutations. These results illustrated that in the ATRA-ATO era, both clinical parameters and molecular markers confer a prognostic value, and the incorporation of these indicators into the risk stratification system allows more accurate prediction of relapse and survival, as well as prompt management of ED risk in APL patients.

In conclusion, this study is based on a large cohort of APL under real-world conditions, which provides compelling evidence that the current ATRA-ATO-based combination strategy is capable of preventing a subset of patients from early death, improving the probability of overall and disease-free survival, and simultaneously reducing the toxicity of chemotherapy. Clinical and molecular features including age, higher WBC count, and *NRAS* mutations can complement the widely-used Sanz risk stratification, and lend additional data informing better management of the disease.

Authors contribution

SY, CWY and **LXJ** conceived and designed the study. **STF, DYE, CWY** and **LXJ** collected the data. **STF** and **LXJ** analyzed the data. **STF** and **CWY** wrote the manuscript. SY revised the paper. All authors reviewed the data and paper, and approved the final version of the manuscript.

Data sharing statement

Data are available from the corresponding author on reasonable request.

Supplementary materials

The online version of this article contains supplementary material, which is available to authorized users.

Declaration of Competing Interest

All authors declare no competing interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tranon.2022.101522.

References

[1] Z.Y. Wang, G.L. Sun, J.X. Lu, L.J. Gu, M.E. Huang, S.R. Chen, Treatment of acute promyelocytic leukemia with all-trans retinoic acid in China, Nouv. Rev. Fr. Hematol. 32 (1) (1990) 34–36.

[2] M.E. Huang, Y.C. Ye, S.R. Chen, J.R. Chai, J.X. Lu, L. Zhoa, et al., Use of all-trans retinoic acid in the treatment of acute promyelocytic leukemia, Blood 72 (2) (1988) 567–572.

[3] Z.X. Chen, Y.Q. Xue, R. Zhang, R.F. Tao, X.M. Xia, C. Li, et al., A clinical and experimental study on all-trans retinoic acid-treated acute promyelocytic leukemia patients, Blood 78 (6) (1991) 1413–1419.
[4] M.A. Sanz, G. Martín, C. Rayón, J. Esteve, M. González, J. Díaz-Mediavilla, 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 94 (9) (1999) 3015–3021.
[5] F. Mandelli, D. Diverio, G. Avvisati, A. Luciano, T. Barbui, C. Bernasconi, 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 90 (3) (1997) 1014–1021.
[6] P. Fenaux, C. Chastang, S. Chevret, M. Sanz, H. Dombret, E. Archimbaud, 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 94 (4) (1999) 1192–1200.
[7] Z.X. Shen, G.Q. Chen, J.H. Ni, X.S. Li, S.M. Xiong, Q.Y. Qiu, et al., Use of arsenic trioxide (As_2O_3) in the treatment of acute promyelocytic leukemia (APL): II. Clinical efficacy and pharmacokinetics in relapsed patients, Blood 89 (9) (1997) 3354–3360.
[8] C. Niu, H. Yan, T. Yu, H.P. Sun, J.X. Liu, X.S. Li, et al., Studies on treatment of acute promyelocytic leukemia with arsenic trioxide: remission induction, follow-up, and molecular monitoring in 11 newly diagnosed and 47 relapsed acute promyelocytic leukemia patients, Blood 94 (10) (1999) 3315–3324.
[9] G.Q. Chen, X.G. Shi, W. Tang, S.M. Xiong, J. Zhu, X. Cai, et al., Use of arsenic trioxide (As_2O_3) in the treatment of acute promyelocytic leukemia (APL): I. As_2O_3 exerts dose-dependent dual effects on APL cells, Blood 89 (9) (1997) 3345–3353.
[10] H.H. Zhu, D.P. Wu, X. Du, X. Zhang, L. Liu, J. Ma, et al., Oral arsenic plus retinoic acid versus intravenous arsenic plus retinoic acid for non-high-risk acute promyelocytic leukaemia: a non-inferiority, randomised phase 3 trial, Lancet Oncol. 19 (7) (2018) 871–879.
[11] H.H. Zhu, X.J. Huang, Oral arsenic and retinoic acid for non-high-risk acute promyelocytic leukemia, N. Engl. J. Med. 371 (23) (2014) 2239–2241.
[12] Z.X. Shen, Z.Z. Shi, J. Fang, B.W. Gu, J.M. Li, Y.M. Zhu, et al., All-trans retinoic acid/As2O3 combination yields a high quality remission and survival in newly diagnosed acute promyelocytic leukemia, Proc. Natl. Acad. Sci. U. S. A. 101 (15) (2004) 5328–5335.
[13] F. Ravandi, E. Estey, D. Jones, S. Faderl, S. O'Brien, J. Fiorentino, et al., Effective treatment of acute promyelocytic leukemia with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab ozogamicin, J. Clin. Oncol. 27 (4) (2009) 504–510.
[14] B.L. Powell, B. Moser, W. Stock, R.E. Gallagher, C.L. Willman, R.M. Stone, et al., Arsenic trioxide improves event-free and overall survival for adults with acute promyelocytic leukemia: North American Leukemia Intergroup Study C9710, Blood 116 (19) (2010) 3751–3757.
[15] F. Lo-Coco, L. Di Donato, R.F. Schlenk, Targeted therapy alone for acute promyelocytic leukemia, N. Engl. J. Med. 374 (12) (2016) 1197–1198.
[16] F. Lo-Coco, G. Avvisati, M. Vignetti, C. Thiede, S.M. Orlando, S. Iacobelli, et al., Retinoic acid and arsenic trioxide for acute promyelocytic leukemia, N. Engl. J. Med. 369 (2) (2013) 111–121.
[17] E. Estey, G. Garcia-Manero, A. Ferrajoli, S. Faderl, S. Verstovsek, D. Jones, et al., Use of all-trans retinoic acid plus arsenic trioxide as an alternative to chemotherapy in untreated acute promyelocytic leukemia, Blood 107 (9) (2006) 3469–3473.
[18] A.K. Burnett, N.H. Russell, R.K. Hills, D. Bowen, J. Kell, S. Knapper, 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. 16 (13) (2015) 1295–1305.
[19] J. Hu, Y.F. Liu, C.F. Wu, F. Xu, Z.X. Shen, Y.M. Zhu, 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. 106 (9) (2009) 3342–3347.
[20] L. Chen, H.M. Zhu, Y. Li, Q.F. Liu, Y. Hu, J.F. Zhou, et al., Arsenic trioxide replacing or reducing chemotherapy in consolidation therapy for acute promyelocytic leukemia (APL2012 trial), Proc. Natl. Acad. Sci. U. S. A. 118 (6) (2021).
[21] M.A. Sanz, F. Lo Coco, G. Martín, G. Avvisati, C. Rayón, T. Barbui, 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 96 (4) (2000) 1247–1253.
[22] J.H. Park, B. Qiao, K.S. Panageas, M.J. Schymura, J.G. Jurcic, T.L. Rosenblat, et al., Early death rate in acute promyelocytic leukemia remains high despite all-trans retinoic acid, Blood 118 (5) (2011) 1248–1254.
[23] S. Lehmann, A. Ravn, L. Carlsson, P. Antunovic, S. Deneberg, L. Möllgård, et al., Continuing high early death rate in acute promyelocytic leukemia: a population-based report from the Swedish adult acute leukemia registry, Leukemia. 25 (7) (2011) 1128–1134.
[24] L.C.S. Thuler, M.S. Pombo-de-Oliveira, Acute promyelocytic leukaemia is highly frequent among acute myeloid leukaemias in Brazil: a hospital-based cancer registry study from 2001 to 2012, Ann. Hematol. 96 (3) (2017) 355–362.
[25] K. Paulson, A. Serebrin, P. Lambert, J. Bergeron, J. Everett, A. Kew, et al., Acute promyelocytic leukaemia is characterized by stable incidence and improved survival that is restricted to patients managed in leukaemia referral centres: a pan-Canadian epidemiological study, Br. J. Haematol. 166 (5) (2014) 660–666.
[26] R. Abrahão, R.C. Ribeiro, B.C. Medeiros, R.H. Keogh, T.H. Keegan, Disparities in early death and survival in children, adolescents, and young adults with acute promyelocytic leukemia in California, Cancer 121 (22) (2015) 3990–3997.
[27] H. Zhu, J. Hu, L. Chen, W. Zhou, X. Li, L. Wang, et al., The 12-year follow-up of survival, chronic adverse effects, and retention of arsenic in patients with acute promyelocytic leukemia, Blood 128 (11) (2016) 1525–1528.
[28] Y. Lou, Y. Ma, S. Suo, W. Ni, Y. Wang, H. Pan, et al., Prognostic factors of patients with newly diagnosed acute promyelocytic leukemia treated with arsenic trioxide-based frontline therapy, Leuk. Res. 39 (9) (2015) 938–944.
[29] A.R. Lucena-Araujo, H.T. Kim, R.H. Jacomo, R.A. Melo, R. Bittencourt, R. Pasquini, 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. 93 (12) (2014) 2001–2010.
[30] X. Lin, N. Qiao, Y. Shen, H. Fang, Q. Xue, B. Cui, et al., Integration of genomic and transcriptomic markers improves the prognosis prediction of acute promyelocytic leukemia, Clin. Cancer Res. 27 (13) (2021) 3683–3694.
[31] R.E. Gale, R. Hills, A.R. Pizzey, P.D. Kottaridis, D. Swirsky, A.F. Gilkes, et al., Relationship between FLT3 mutation status, biologic characteristics, and response to targeted therapy in acute promyelocytic leukemia, Blood 106 (12) (2005) 3768–3776.
[32] L. Cicconi, M. Divona, C. Ciardi, T. Ottone, A. Ferrantini, S. Lavorgna, 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 30 (10) (2016) 1987–1992.
[33] E. Barragán, P. Montesinos, M. Camos, M. González, M.J. Calasanz, J. Román-Gómez, et al., Prognostic value of FLT3 mutations in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and anthracycline monochemotherapy, Haematologica 96 (10) (2011) 1470–1477.
[34] H.H. Zhu, Y.F. Ma, K. Yu, G.F. Ouyang, W.D. Luo, R.Z. Pei, et al., Early death and survival of patients with acute promyelocytic leukemia in ATRA plus arsenic era: a population-based study, Front. Oncol. 11 (2021), 762653.