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Early death and intracranial hemorrhage prediction in acute promyelocytic leukemia: validation of a risk score in a chemotherapy plus ATRA cohort from an international consortium

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Early death and intracranial hemorrhage prediction in acute promyelocytic leukemia: validation of a risk score in a chemotherapy plus ATRA cohort from an international consortium

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Running title: Bleeding and early death prediction in APL

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Authors' contributions: WFS acquired and interpreted data and performed the statistical analysis. HTK reviewed the statistical analyses. SU, JRN, VS, PM, and EMR were the National Coordinators of ICAL in Chile, Peru, Paraguay, Uruguay, and Brazil, respectively, and contributed to the development of the clinical network, the oversight of laboratory and management procedures, data acquisition and interpretation. RAMM, ABFG, KP, ECN, RIB, NR, SQ, AAL, CO, LLFP, FT, FM, PM, EMF, BKLD, PD and JU were responsible for centers performing the diagnosis and treatment of patients and acquired data. MT, RR, AG, RD, PJMV, MS, BL, NB, HTK and EMR contributed to the conception and design of the work,

interpreted data, and drafted the manuscript. All authors have critically reviewed and approved the manuscript.

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To the editor:

Acute promyelocytic leukemia (APL) is a distinctive subtype of acute myeloid leukemia characterized by excellent cure rates after frontline therapy, based on all-trans retinoic acid (ATRA) and arsenic trioxide (ATO).[1] In clinical practice, this disease usually presents with a peculiar coagulopathy, marked by primary hyperfibrinolysis and high incidence of early fatal bleeding events.[2] Therefore, early death (ED), which is defined as death occurring within the first 30 days from diagnosis, is the most common cause of treatment failure.[3] Long term survival rates reported in "real-world" retrospective studies range from 60 to 80%, while overall survival (OS) reported in pivotal clinical trials of APL usually exceeds 90%.[3–5] A recent publication from Österroos[6] et al. introduced a new risk score for ED in APL, based on 3 baseline parameters – age, platelet, and white blood cell counts (WBC). This study reported an ED rate of 4.8%, 20.2%, and 50.9% in patients from Swedish registry with low, high, and very high-risk ED score, respectively. This cohort comprised patients treated with ATRA plus chemotherapy or arsenic trioxide (ATO), depending on the time of diagnosis.[6] Here, we present an analysis in a cohort of patients from Latin America, treated prospectively with ATRA plus daunorubicin within the International Consortium in APL (IC-APL).[7]

The issue of early mortality in APL appears to be even more severe in resource-limited healthcare settings, where delayed recognition of APL and limited access to ATRA or blood transfusion in remote areas are reported.[4] Intracranial hemorrhage (ICH) is the most common site of bleeding in APL, and plays a significant role in early mortality.[4,8,9] In these cases, patients are commonly diagnosed in a poor clinical condition, unable to receive adequate antileukemic therapy, and frequently die from neurological complications.

In 2005, the IC-APL trial was initiated in Brazil, Mexico, Chile and Uruguay, aiming at increasing cure rates of APL in Latin America, as well as creating a cooperative diagnostic and therapeutic network of institutions in developing countries.[7] In 183 patients previously reported, an early death rate of 15% had been found, much lesser than previous retrospective values reported by these centers.[5,7] Although ICH is already acknowledged as a frequent event in APL, there are few studies specifically evaluating this complication. Herein, we aimed to validate the ED risk score in our population, and to analyze the impact of ICH at diagnosis, and risk factors for its occurrence in a large cohort of APL patients enrolled into IC-APL.

The data from the IC-APL registry includes patients newly diagnosed with APL between March/2005 and March/2020. The IC-APL study protocol has been described elsewhere (figure S1, supplementary material). [7,10] Patients had their diagnosis confirmed by the presence of PML-RARA as previously described.[7] Laboratory data were collected at baseline. The protocol recommended that all patients undergo testing for renal and hepatic function (creatinine, urea, aminotransferases, bilirubin), coagulation parameters (fibrinogen, PT, and aPTT), as well as a complete blood count, pregnancy test, and serology for HBV, HCV, and HIV. All ICH cases had their diagnosis confirmed by head computed tomography (CT) scan, indicated by the treating physician in case of clinical suspicion. Central nervous system prophylaxis was not given. Local ethics committees from the participating institutions have approved this study.

Among 1004 subjects screened, 813 patients were eligible to the treatment protocol and were included in this analysis. Main reasons for ineligibility were treatment with other protocols (48.7%), negative PML-RARA (12.2%), and age (10.7%). Some patients died before receiving ATRA (n=13) and were also not included in the cohort (6.5%). Among these, 10/13 presented with severe ICH and did not receive any antileukemic treatment. Other reasons are detailed in the original publication.[10]

Overall, median age was 35 years old (range, 15-74). Ten percent of patients presented with an ECOG Performance Status Scale >2. Most patients presented with symptoms that had been ongoing for more than 10 days (44.7%). Variant hypogranular morphology was reported in 10.4%, while Sanz[11] relapse risk score was low, intermediate, and high in 10.9%, 52.3%, and 36.8% of subjects, respectively. ED rate was 14% (112/813, 95% confidence interval [95% CI], 11.7-16.6). Bleeding was the major cause of ED in those patients (60.5%), followed by infection (25.4%). Differentiation syndrome occurred in 37% of patients who died within 30 days, but it was only registered as the cause of death in 5.3% of cases. ICH represented the most common site of hemorrhagic events (36% of ED patients), followed by bleedings at pulmonary (11.4%), and gastrointestinal sites (9.6%). All bleeding events occurred within 30 days from diagnosis. Acute kidney injury (AKI) of any grade was detected in 13.1% during induction, being grade 3 or 4 in 5%.

When the aforementioned ED risk score was applied to the IC-APL cohort, it divided the cohort in three distinct categories – low (n=392, 48.5%), high (n=344, 42.6%), and very high risk (n=72, 8.9%), with ED rates of 5.9%, 18.3%, and 37.5%, respectively (figure 1). Overall rate of ICH was 8.2% (67/813), with ICH rates being 4.8%, 12.8%, and 17.1% in patients with low, high, and very high ED risk score (figure 2). ED rate in patients with ICH was 61.2%, with two more deaths occurring after 30 days from diagnosis.

Univariate analysis for CNS bleeding in this cohort showed an association ($p<0.05$) with various severity parameters, such as the variant morphological subtype, initial hemoglobin, WBC, and creatinine levels. The incidence of ICH in patients with WBC>$10x10^9$/L and variant morphology was 21.3%. A multivariable adjustment of these factors with the ED Risk Score is presented in table 1. After excluding those patients who died within 30 days from diagnosis, ICH did not impact on OS (Hazard ratio [HR]=1.55 [95% CI 0.374-6.45], p=0.544) but impacted on relapse-free survival (RFS) (HR=2.23, [95% CI 1.09-4.56, p=0.028). By competing risk analysis, an impact could be seen in relapse incidence (HR 2.43 [95% CI 1.04-5.70], p=0.041), while there was no impact on non-relapse mortality after 30 days (HR 1.44 [95% CI 0.34-6.02], p=0.62). This impact remained significant even after adjusting for Sanz relapse risk score (adjusted HR = 2.47 [95% CI 1.05-5.78], p=0.037). Out of 93 relapses, only 9 presented concomitant central nervous disease (CNS). Among these 9 CNS relapses, only 1 had presented with ICH at the diagnosis. Long-term outcomes of whole IC-APL cohort were reported elsewhere.[10]

In this report, we validated the ED risk score previously published in a large Latin American prospective cohort (IC-APL), for predicting early outcomes in APL.[6] Its validated utility

in predicting early outcomes in APL strengthens its basis for facilitating tailored interventions to mitigate mortality risks, such as the implementation of differential transfusion triggers or newer agents in this early scenario. Also, the increasing prevalence of bleeding in these high-risk patients may lead to early screening of higher risk patients with mild or no neurological symptoms for ICH with cranial CT, aiming to early diagnose this complication and intervene promptly. The increasing prevalence of bleeding in these high-risk patients may prompt early screening for ICH in patients with mild or no neurological symptoms, using cranial CT, with the aim of diagnosing this complication early and enabling prompt intervention. Furthermore, it should be recognized that the incidence of ICH may be underestimated in prospective registry studies, as some patients arrive in the emergency room in such critical condition that further therapy is not possible.

In the IC-APL, the multivariable logistic regression model has shown that age ≥ 40 years, ECOG performance status of 3, high-risk Sanz relapse category, bcr3 PML/RARA isoform, time interval from symptom onset to diagnosis longer than 48 hours, ICH, and pulmonary bleeding were statistically associated with ED.[10] Comparatively with the ED score just reported, in our cohort, only age and WBC were predictive of ED, while platelet counts did not reach statistical significance in the reported model.[10] This also underscores that the Sanz relapse risk score was originally reported for predicting relapse after remission is achieved, rather than ED. The PETHEMA group itself demonstrated in prior publications from the LPA96 and LPA99 trials that creatinine level, WBC, peripheral blood blast count, age, and male sex were associated with ED in these cohorts.[12] In children and adolescents with newly diagnosed APL, a multivariable model demonstrated that high WBC count and obesity were independently associated with ED.[13] In Latin America, the proportion of high-risk patients is higher, possibly due to delayed diagnosis and intrinsic biological differences.[4,5]

This study also demonstrated that ICH within 30 days of diagnosis may lead to APL relapses after induction therapy. This had already been demonstrated by the PETHEMA group regarding CNS relapses, where its incidence in patients who presented ICH at diagnosis was 18.7%.[14] Kulkarni et al.[15] has demonstrated that, when using an ATO-based approach, relapses do not increase in patients who presented with ICH, which might translate the augmented disease control with ATO and an increased CNS penetration for this drug.[1] The role of intrathecal chemotherapy and high-dose cytarabine in preventing CNS disease is unclear, especially in the current scenario of ATO-based regimens.[1] Guidelines still have recommended intrathecal chemotherapy for patients with ICH at presentation.[1]

In conclusion, our study underscores the critical role of early mortality risk assessment in APL and highlights the significant impact of ICH on both short-term and long-term outcomes. These insights pave the way for future studies aimed at optimizing APL treatment approaches and improving patient outcomes. The current IC-APL2020 employs ATRA plus oral ATO for frontline APL treatment, with the expectation of reducing early toxicity and disease relapses in the coming years.

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Tables and figures

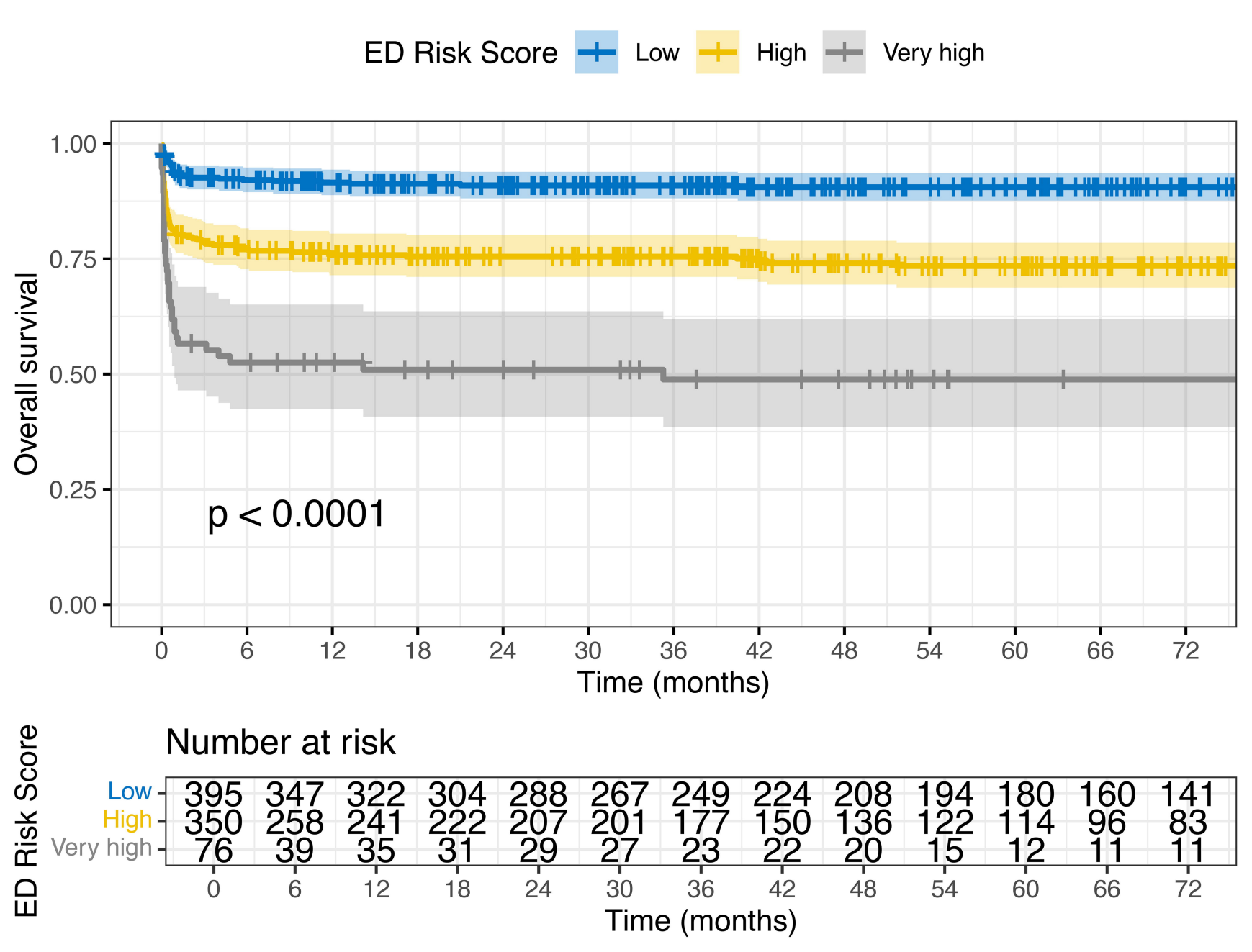
Table 1. Multivariable adjusting of baseline variable for intracranial hemorrhage in APL			
	Odds Ratio	**95% Confidence interval**	**p-value**
Variant morphology	1.330	0.458-3.290	0.5648
Hemoglobin (g/dl)	0.926	0.801-1.068	0.2965
ED Risk Score			
- Low	reference		
- High	1.586	0.752-3.426	0.2284
- Very high	2.621	0.930-6.951	0.0576
Creatinine	1.767	1.113-2.952	0.0171
WBC (x10^9/L)	1.007	1.001-1.013	0.0284

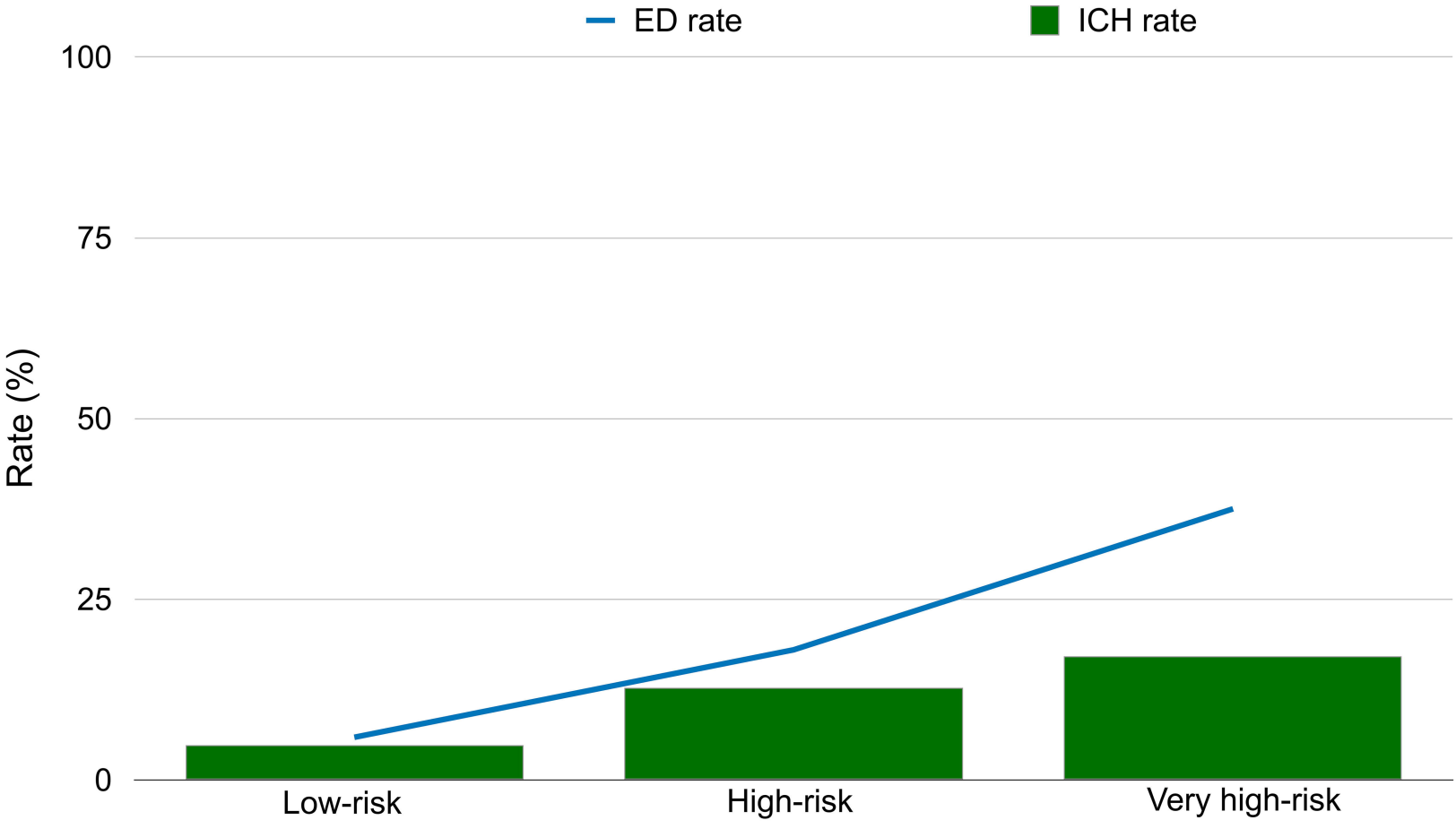
ED: early death; WBC: white blood cell count

Figure legends.

Figure 1. Overall survival for low, high, and very high-risk early death score in patients from International Consortium for acute promyelocytic leukemia.

Figure 2. Proportions of ICH (intracranial hemorrhage) and ED (early death) according to ED Risk Score in IC-APL cohort.


ED Risk Score
Low
High
Very high
Overall survival
1.00
0.75
0.50
0.25
0.00
p < 0.0001
0
6
12
18
24
30
36
42
48
54
60
66
72
Time (months)
Number at risk
ED Risk Score
Low 395 347 322 304 288 267 249 224 208 194 180 160 141
High 350 258 241 222 207 201 177 150 136 122 114 96 83
Very high 76 39 35 31 29 27 23 22 20 15 12 11 11
0
6
12
18
24
30
36
42
48
54
60
66
72
Time (months)


ED rate
ICH rate
100
75
50
25
0
Rate (%)
Low-risk
High-risk
Very high-risk

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Supplementary appendix

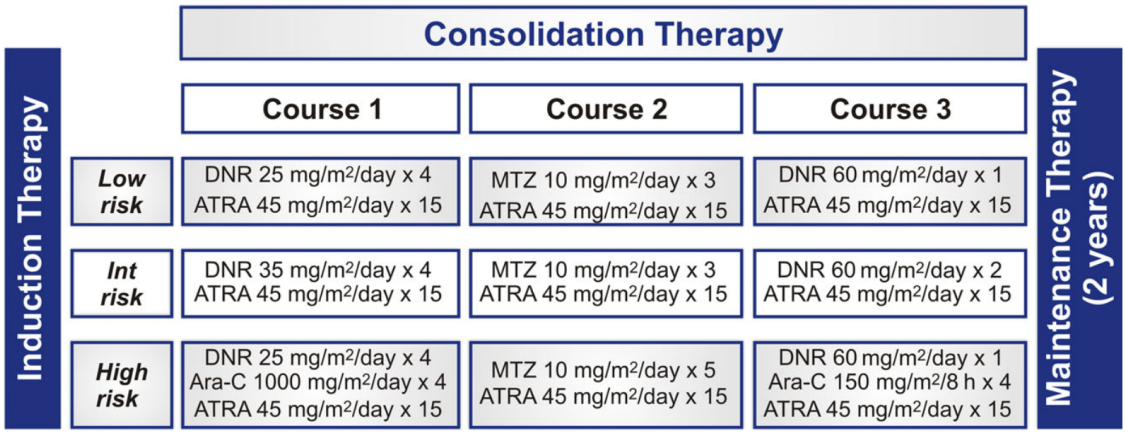

Figure S1. IC-APL treatment regimen. Ara-C, cytarabine; ATRA, all trans retinoic acid; DNR, daunorubicin; IC-APL, International Consortium on