



Incident adverse events following therapy for acute promyelocytic leukemia

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ABSTRACT

The use of all-trans retinoic acid (ATRA) combined with arsenic trioxide (ATO) with or without cytotoxic chemotherapy is highly effective in acute promyelocytic leukemia (APL) but incident chronic adverse events (AEs) after initiation of therapy are not well understood. We retrospectively analyzed adult patients with newly diagnosed APL from 2004 through 2014 to identify incident AEs following treatment and contributing risk factors. Cardiac and neurologic AEs were more common and characterized in detail. Cardiac AEs such as the development of coronary artery disease (CAD), arrhythmias, and heart failure had a cumulative incidence of 6.4% (CI95 1.8–11.1%), 2.9% (CI95 0.0–6.4%), 5.8% (CI95 1.2–10.3%) at 4 years from diagnosis, respectively. In multivariate analyses of factors influencing heart failure, the presence of clinical or radiographic CAD (HR 4.25; $P = 0.011$) or troponin elevation prior to completion of therapy (HR 8.86; $P = 0.0018$) were associated with increased heart failure incidence, but not anthracycline use or dose. Neurological AEs were common following therapy; at 4 years, the cumulative incidence of vision changes was 12.4% (CI95 6.0–18.7%), peripheral neuropathy 10.3% (CI95 4.5–16.1%), and memory or cognitive change 7.6% (CI95 2.5–12.7%). We did not identify any association between specific therapies and the development of cardiac and neurologic AEs. APL is a highly curable leukemia; further efforts are needed to address incident chronic AEs, with particular focus on cardiac and neurologic care.

1. Introduction

Acute promyelocytic leukemia (APL) is characterized by the presence of a translocation between chromosome 15 and 17 [t(15;17)], resulting in a novel gene fusion, *PML-RARA* and subsequent leukemia [1]. Advances in the management of APL, including the use of chemotherapy regimens incorporating all-trans retinoic acid (ATRA) and arsenic (ATO), have made this a highly curable subtype of leukemia [2–4]. Nonetheless, the extent and characterization of chronic adverse events (AEs) following treatment in these patients is not well understood. The use of ATRA and ATO in APL patients has been reported to have a minimal chronic AE profile [5], but others have reported AEs such as cardiac dysrhythmia, and peripheral neuropathy [6]. Furthermore, although significant arsenic retention was not detected in plasma, urine, hair, and nails of ATO-treated patients during a 12-year follow-up, animal models suggest that these are not good predictors of tissue arsenic deposition in solid organs such as the brain [7]. Finally, depending on the risk of APL, cytotoxic chemotherapy such as anthracyclines may be incorporated, which may add additional chronic

cardiac AEs. It remains unclear how AEs after treatment for APL may vary according to prior treatments. As more patients are cured of their APL, there is increased importance of improving survivorship outcomes.

In this analysis, we retrospectively assess adult patients treated for APL to characterize incident AEs following treatment and according to types of therapy. Cardiovascular and neurologic AEs were found to have the highest prevalence following therapy, and were characterized in detail.

2. Materials and methods

Institutional review board approval was obtained and research was conducted in accordance with the Helsinki declaration. We retrospectively identified adult patients age 18 or older with newly-diagnosed APL between 2004 and 2014 at Massachusetts General Hospital and Brigham and Women's Hospital. Diagnosis was based on molecular and/or cytogenetic confirmation of *PML/RARA* fusion transcript and pathologic features. We collected information regarding the date of

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diagnosis, patient race and sex, age at diagnosis, white blood cell (WBC) and platelet (PLT) count at diagnosis. We also identified baseline cardiac or neurologic co-morbidities prior to the initiation of therapy, as well as the treatment regimens employed. Therapeutic regimens were grouped according to common APL backbones and categorized as a) ATRA + ATO-based per gruppo Italiano malattie ematologiche dell'adulto (GIMEMA) [2], b) ATRA + anthracycline + ATO-based per cancer and leukemia group B (CALBG) 9710 [3], c) ATRA + anthracycline + mitoxantrone-based per programa para el tratamiento de hemopatias malignas (PETHEMA) [4], and d) other regimens which were not clearly defined or clinical trials.

AEs were documented after diagnosis, and extracted from the medical record, including dates of any incident AEs. When the exact date was not available, the date of the first note or lab test confirming the event was used. Coronary artery disease (CAD) was defined as the presence coronary lesions requiring coronary intervention or visualized during coronary angiography, or coronary calcifications demonstrated on computed tomography (CT) imaging. Arrhythmias were documented by physicians and/or confirmed on an electrocardiogram. Congestive heart failure was defined as a reduction in left ventricular ejection fraction (EF) to 50% or below. Vision changes, peripheral neuropathy, and neurocognitive changes were patient-reported and documented by physicians.

Patients were followed from the time of presentation to death or censored at last known follow-up. AEs occurring >6 months from diagnosis were incorporated into the statistical methods unless otherwise indicated. Thus, patients with early deaths were excluded. The cumulative incidence of AEs following APL diagnosis was estimated using the fine and gray method, with relapse and death as competing risks. Overall survival (OS) and progression-free survival (PFS) were estimated by the method of Kaplan and Meier. Cox proportional hazards models were used to perform multivariable analyses. Log-rank tests were used to compare between groups. All analyses were performed using the R v2.15.3 statistical software. P-values are considered significant at a two-sided alpha of 0.05.

3. Results

We identified 115 adult patients with a new diagnosis of APL. Median length of follow-up was 5.3 years (range 0–9.7 years). Patient characteristics are described in Table 1. The median age at diagnosis was 48 years old; 49% of patients were male and 76% identified as white. 31 patients (27%) had a white blood count greater than 10,000/mL and were considered “high risk”.

Pre-existing co-morbidities prior to the diagnosis of APL are outlined in Table 1. Pre-existing cardiac co-morbidities included 12 (10%) patients with CAD and of these, 10 patients had clinically significant CAD requiring active medical management or interventions. Other cardiac co-morbidities included 3 (3%) patients with arrhythmias, 2 (2%) patients with systolic heart failure, 6 (5%) patients with diabetes, and 0 (0%) patients with chronic kidney disease (CKD). Pre-existing neurological co-morbidities were uncommon: 4 (3%) patients had peripheral neuropathy and 2 (2%) patients had memory or cognitive impairments.

OS for all groups was 91.3%, 89.5%, 88.6% at 1, 12, and 24 months, respectively (Fig. 1). PFS was 91.3%, 88.6%, 85.8% at 1, 12, and 24 months, respectively (Fig. 1). Early deaths in 10 patients were related to bleeding (n = 6), respiratory failure (n = 2), liver failure (n = 1), and myocardial infarction (n = 1). Of the 115 patients, 107 (93.0%) achieved complete remission (CR) with initial treatment. 55 patients were treated per the CALBG 9710 protocol [3], 15 were treated per the GIMEMA protocol [2], 18 were treated per the PETHEMA [4], and 27 were treated on other clinical trials or other regimens. All patients received ATRA as the backbone of therapy. For hematopoietic transplantations, 5 were autologous transplants and 3 were allogeneic transplants for relapses. 1 patient received an allogeneic

Table 1
Characteristics of the 115 patients with APL between 2004 and 2014.

Characteristic	Number of patients (Percent)
Age (median, range)	48 years (18–84)
Sex	
Male	56 (49%)
Female	59 (51%)
Race/Ethnicity	
White	88 (76%)
Non-white	28 (24%)
WBC at diagnosis (median, range)	1.9 th/mL (0.3–97.4)
“Higher Risk” WBC > 10,000	31 (27%)
PLT at diagnosis (median, range)	37.0 th/mL (2.0–282.0)
Cardiac co-morbidity at diagnosis	
Coronary artery disease	12 (10%)
Arrhythmia	3 (3%)
Heart failure	2 (2%)
Neurologic co-morbidity at diagnosis	
Peripheral neuropathy	4 (3%)
Memory and/or cognitive issues	2 (2%)
Diabetes mellitus	6 (5%)
Chronic kidney disease	0 (0%)
Treatment	
CALBG 9710	55 (47%)
GIMEMA	15 (13%)
PETHEMA	18 (16%)
Other	27 (23%)
Allogeneic hematopoietic transplantation	4 (3%)
Autologous hematopoietic transplantation	5 (4%)

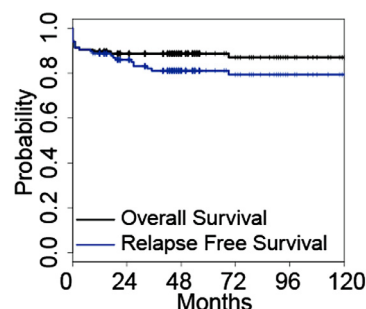


Fig. 1. Overall survival (OS) and relapse free survival (RFS) in APL patients.

Kaplan–Meier curve of OS and RFS demonstrates survival rates consistent with modern treatment strategies.

Table 2
Long-term adverse events in acute promyelocytic leukemia patients.

Adverse events	4-year cumulative incidence (95%CI)
Cardiac	8.4 (1.9–14.8)
CAD	6.4 (1.8–11.1)
Heart failure	5.8 (1.2–10.3)
Cardiac arrhythmia	2.9 (0.0–6.4)
Neurologic	24.3 (13.4–35.2)
Vision changes	12.4 (6.0–18.7)
Peripheral neuropathy	10.3 (4.5–16.1)
Neurocognitive changes	7.6 (2.5–12.7)
Endocrine	4.8 (0.6–9.0)
Gastrointestinal	7.7 (2.6–12.9)
Renal	3.3 (0–6.9)

transplantation for myelodysplastic syndrome.

Cardiac and neurologic AEs had the highest prevalence (Table 2). The cumulative incidence of total cardiac AEs was 8.4% (95% confidence interval [CI95] 1.9–14.8%) at 4 years, consisting of CAD, heart failure, and cardiac arrhythmia. The cumulative incidence of neurologic AEs was 24.3% (CI95 13.4–35.2%) at 4 years, consisting of vision changes, peripheral neuropathy, and neurocognitive changes. The

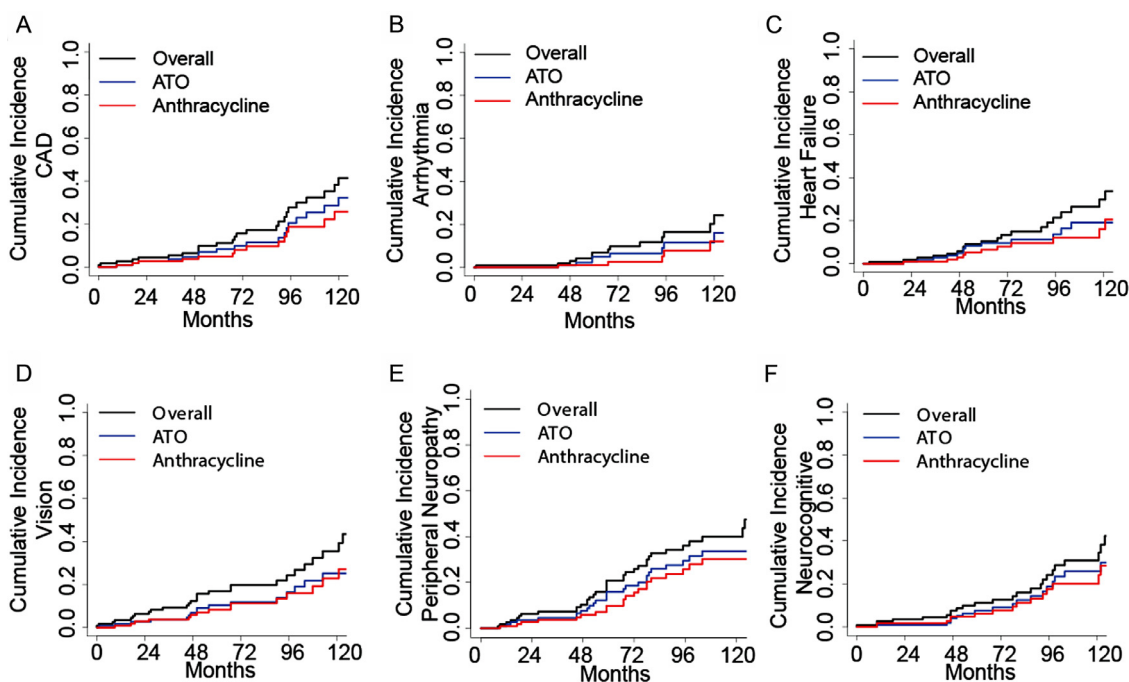


Fig. 2. Cumulative incidence rates for AEs in APL patients.

Cumulative incidence rates are plotted for A) CAD, B) cardiac arrhythmias, C) heart failure, D) vision changes, E) peripheral neuropathy, and F) neurocognitive changes occurring 6 months from diagnosis. Overall rates are plotted in black, ATO containing therapy is plotted in blue, and anthracycline containing therapy is plotted in red. Some regimens may incorporate both ATO and anthracycline therapy, and thus is included in both plots. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

cumulative incidence of endocrine AEs was 4.8% (CI95 0.6–9.0) at 4 years, which consisted mostly of diabetes and hypothyroidism. The cumulative incidence of gastrointestinal AEs was 7.7% (CI95 2.6–12.9) at 4 years, which consisted mostly of gastrointestinal bleeding. The cumulative incidence of renal AEs was 3.3% (CI95 0–6.9) at 4 years.

3.1. Cardiac AEs

Eighteen patients had troponin elevations prior to or during therapy and of these, 10 (56%) patients had associated chest pain, and 4 (22%) had prior documented CAD. Troponin elevations occurred prior to therapy in 6 (33%), during induction in 8 (44%), and during consolidation in 4 (22%) patients. Of the 15 patients who developed CAD after diagnosis of APL, 8 (53%) patients had asymptomatic coronary calcifications on imaging whereas the remaining 7 (47%) had clinical disease. In 4/15 (27%) patients, the discovery of CAD occurred after completion of therapy. The overall cumulative incidence of CAD following therapy was 4.5% (CI95 0.6–8.3%) and 6.4% (CI95 1.8–11.1%) at 2 and 4 years from diagnosis, respectively (Fig. 2A). There was no significant difference in the incidence of atherosclerotic cardiac disease following therapy between patients receiving regimens that incorporate ATO or those that incorporated anthracyclines.

Incident arrhythmias included 11 (79%) patients with atrial fibrillation or flutter, 2 (14%) patients with atrioventricular reentrant tachycardia, and 1 (7%) patient with ventricular tachycardia. In 7/14 (50%) patients, the discovery of arrhythmias occurred after completion of therapy. The cumulative incidence of arrhythmias following therapy was 0.9% (CI95 0.0–2.6%) and 2.9% (CI95 0.0–6.4%) at 2 and 4 years from diagnosis, respectively (Fig. 2B). Multivariate analysis did not reveal an association between ATO use and development of arrhythmias after therapy (HR 1.11; $P = 0.87$), but female sex (HR 4.0; $P = 0.038$) and increasing age (HR 1.07 per year; $P = 0.0004$) were associated with development of cardiac arrhythmias. Other factors not significantly associated included anthracycline use, race, initial WBC or PLT count.

To evaluate incident heart failure, we identified 108 patients who had at least one echocardiogram or radionuclide ventriculography after initiation of chemotherapy; of these, 20 (19%) had a newly depressed EF $\leq 50\%$ consistent with heart failure. Half of these patients had an EF between 40–50% with concurrent evidence of diastolic dysfunction. Of those with heart failure, 9 (45%) patients had New York Heart Association Class II symptoms or higher. In 11/20 (55%) patients, the discovery of heart failure occurred after completion of therapy. Cumulative incidence of heart failure following therapy was 1.8% (CI95 0.0–4.3%) and 5.8% (CI95 1.2–10.3%) at 2 and 4 years from diagnosis, respectively (Fig. 2C). Multivariate analysis revealed that the presence of pre-existing radiographic or clinical CAD was significantly associated with development of heart failure during therapy (HR 11.2; $P = 0.011$) or after therapy (HR 16.76; $P = 0.044$) (overall HR 4.25; $P = 0.011$; Table 3). Troponin elevation at diagnosis or during therapy was similarly associated with development of heart failure (HR 8.86; $P = 0.0018$). Interestingly, anthracycline exposure and the cumulative dose of either daunorubicin or idarubicin were not associated with increased risk. Idarubicin use was associated with lower incidence of heart failure (HR 0.98 per mg/m^2 ; $P = 0.017$). There were no significant associations between development of heart failure and other patient characteristics including age, female sex, race, and baseline white blood cell (WBC) or platelet (PLT) count, and baseline arrhythmias, chronic kidney disease (CKD), or diabetes mellitus.

3.2. Neurologic AEs

Incident neurologic AEs following treatment included vision changes, peripheral neuropathy, and cognitive changes. Of the total 30 patients with incident vision complaints, 6 (20%) were clinically reported as related to APL: 4 (13%) patients had retinal hemorrhages documented by an ophthalmologist and 2 (7%) had vision changes related to late central nervous system relapse. Eight (27%) patients had vision changes of unclear etiology. The remaining 16 (53%) patients had vision changes that were clinically not felt to be related to APL

Table 3

Risk factors for developing heart failure in APL patients. Heart failure diagnoses detected within 6 months of APL diagnosis are noted in the leftmost columns, and those detected afterwards are noted on the middle columns. * denotes significant P-values.

Onset	<6 months		>6 months		All	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (per year)	0.99 (0.96,1.02)	0.70	1.04 (1,1.08)	0.31	1.02 (1,1.04)	0.24
Sex						
Male	1		1		1	
Female	4.18 (3.35,5.01)	0.08	0.78 (−0.58,2.14)	0.85	0.8 (0.23,1.36)	0.69
Race/Ethnicity						
White	1		1		1	
Non-white	0.80 (0.22,1.56)	0.75	2.15 (0.97,3.33)	0.52	1.39 (0.63,2.14)	0.67
WBC at diagnosis (per th/mL)	0.99 (0.95,1.02)	0.75	1 (0.95,1.05)	0.96	1.01 (0.99,1.04)	0.57
PLT at diagnosis (per th/mL)	1 (1,1)	0.29	1 (0.99,1.01)	0.82	1 (1,1.01)	0.63
Therapy						
ATO use	0.26 (−0.52,1.03)	0.08	0.15 (−1.48,1.78)	0.24	1.08 (0.34,1.81)	0.92
Anthracycline use	4.82 (3.5,6.14)	0.23	0.02 (−3.45,3.49)	0.26	1.26 (0.02,2.5)	0.85
Daunorubicin dose (per mg/m ²)	1.0 (0.99,1)	0.26	1.01 (1,1.02)	0.21	1 (0.99,1)	0.19
Idarubicin dose (per mg/m ²)	1.0 (0.99,1.01)	0.93	0.97 (0.94,1)	0.37	0.98 (0.96,0.99)	0.017*
Troponin elevation	4.13 (3.3,4.96)	0.09	4.78 (3.53,6.03)	0.21	8.86 (8.16,9.56)	0.0018*
Coronary artery disease	11.2 (10.25,12.15)	0.011*	16.76 (15.36,18.16)	0.044*	4.25 (3.68,4.82)	0.011*
Arrhythmia	NA	NA	15.94 (13.55,18.33)	0.25	0.64 (−0.47,1.74)	0.68
Chronic kidney disease	NA	NA	1.49 (−1.24,4.22)	0.88	1.97 (0.72,3.23)	0.59
Diabetes Mellitus	NA	NA	19.39 (16.72,22.06)	0.27	3.71 (2.59,4.82)	0.24

including those due to cerebrovascular accidents occurring after therapy for APL, cataracts, refraction-related disease, diabetic retinopathy, cranial nerve palsies, and macular degeneration. In 9/30 (30%) patients, vision changes were reported after completion of therapy. The cumulative incidence of vision changes following therapy was 6.3% (CI95 1.8 – 10.8%) and 12.4% (CI95 6.0–18.7%) at 2 and 4 years from diagnosis, respectively (Fig. 2D).

Of the 36 with incident neuropathy, 18 (50%) patients had grade 2 neuropathy, 1 (3%) patient had grade 3 neuropathy and, 17 (47%) patients did not have clear documentation. Of the patients with neuropathy, 10 had active diabetes but there was no significant association. In 17/36 (47%) patients with neuropathy, neuropathy occurred after completion of therapy. The cumulative incidence of peripheral neuropathy following therapy was 6.3% (CI95 1.8–10.9%) and 10.3% (CI95 4.5–16.1%) at 2 and 4 years from diagnosis, respectively (Fig. 2E). There were no significant differences in incidence of neuropathy between patients receiving ATO or anthracycline therapy.

A total of 27 patients experienced incident neurocognitive deficits, and of these, 23 (85%) patients complained of memory loss, specifically short-term memory, and 4 (15%) patients complained of difficulties with higher executive function. 15 (55%) patients had a referral to psychiatry or neurology for further evaluation, and 8/15 (53%) had a neurological evaluation that confirmed the diagnosis. Two patients were referred for a full neurocognitive evaluation. Of the 27 affected, 2 patients had prior intracranial bleeds during APL treatment, and 2 patients had cerebrovascular accidents after therapy. In 13/27 (48%) patients, neurocognitive changes were reported after completion of therapy. The estimated cumulative incidence of neurocognitive changes following therapy were 3.6% (CI95 0.1–7.0%) and 7.6% (CI95 2.5–12.7%) at 2 and 4 years from diagnosis, respectively (Fig. 2F). In multivariate analysis, there was no significant association with particular therapy, gender, age, race, and presenting WBC or PLT counts. Furthermore, receiving ATRA/ATO based therapy without concurrent cytotoxic chemotherapy did not appear to significantly alter this risk (HR 0.31, $P = n.s.$).

4. Discussion

Although APL is a highly curable form of leukemia, patients experience a significant number of cardiac and neurologic AEs during and following treatment. Here, we identified incident chronic AEs and their contributing risk factors in APL patients. Overall, CAD was the leading

cardiac co-morbidity at diagnosis. Development of heart failure appeared to be strongly associated with pre-existing CAD in multivariate analysis. Neurologic AEs included vision changes, peripheral neuropathy, and neurocognitive changes, especially worsening of short-term memory.

CAD was the leading cardiac co-morbidity in APL patients at diagnosis, with 10% of patients having baseline CAD (Table 1). Emerging data suggests that aberrant clonal hematopoiesis is associated with a 2-fold higher risk of CAD [8,9] but whether this applies to APL patients requires further investigation as these mutations are infrequent in APL. Although the prevalence of CAD was relatively common at diagnosis of APL, perhaps speaking to the age of the patient cohort, specific APL therapies did not appear to be associated with incident CAD following treatment. Previous studies suggested that ATO poisoning may be associated with CAD [10], but we did not find any significant association with ATO doses used in APL therapy and the development of CAD.

ATO can prolong corrected QT (QTc) prolongation intervals, and caution is warranted during its use [6]. In animal models, deposition of ATO in cardiac tissues has been seen and may lead to structural abnormalities after ingestion of ATO [11]. In the current analysis, ATO therapy was not significantly associated with the development of other arrhythmias. Instead, known risk factors such as female gender (HR 4.0; $P = 0.038$), and increasing age (HR 1.07 per year; $P = 0.0004$), were significantly associated. No cases of torsades des pointes were seen.

A frequently encountered cardiac event following therapy was incident heart failure, reaching 5.8% (CI95 1.2–10.3%) at 4 years. Anthracycline use during induction and consolidation therapy is a known risk factor for cardiomyopathy [12], as are other clinical factors such as increasing age, mediastinal radiation, female gender in the pediatric population, and hypertension [12]. In our APL population, the presence of CAD, whether clinically significant or imaging-based, was the greatest risk factor for the development of subsequent heart failure (Table 3). Furthermore, although CAD may be difficult to diagnose at initial APL presentation, troponin elevation at diagnosis or during therapy was also an independent risk factor for development of heart failure (HR 8.86; $P = 0.0018$). Interestingly, in the current analysis, the use of and cumulative dose of anthracyclines as well as other patient characteristics such as age, gender, race, history of arrhythmia, chronic kidney disease, or diabetes mellitus were not significantly associated with increased incident heart failure, although patient numbers were perhaps too small to detect an association. Idarubicin use was associated with lower risk of heart failure [13], but further studies are

needed to confirm this. It may therefore be clinically meaningful to develop monitoring and treatment strategies for prevention of heart failure in APL patients with pre-existing CAD or with troponin elevations.

Zhu et al. published a 12-year follow-up study of the chronic long-term survival and chronic AEs in 112 patients treated with arsenic trioxide (ATO) and all-trans retinoic acid (ATRA) [5]. In their study, AEs involving the cardiovascular system were not observed perhaps due to lack of significant CAD in their population. Other AEs such as the development of CAD or arrhythmias was not clearly associated with ATRA/ATO therapy in our analysis.

Several neurological AEs were documented in APL patients including vision changes, peripheral neuropathy, and neurocognitive defects, particularly short-term memory loss. Aside from the late central nervous system relapses, most vision changes occurred early before therapy or during therapy. Only 19% of patients with early vision changes had changes that were clearly attributed to APL, which include retinal hemorrhages and cerebrovascular accidents due to coagulopathy, but this is perhaps related to under-diagnosis. Peripheral neuropathy was the most common neurological complaint with cumulative incidence of 10.3% (CI95 4.5–16.1%) at 4 years. A drawback of analysis of peripheral neuropathy is that severity is often not well-documented.

Interestingly, we found an increasing cumulative incidence of neurocognitive deficits to 7.6% (CI95 2.5–12.7%) at 4 years. 85% of the patients with neurocognitive deficits complained of difficulty with short-term memory. Cognitive impairment associated with chemotherapy is increasingly recognized, such as in patients receiving adjuvant treatment for breast cancer [14]. In acute lymphoblastic leukemia (ALL) in children, late neurocognitive effects are observed in a 20–50% of patients; in these patients, it may relate to genetic polymorphisms in the metabolism of methotrexate (MTX) [15]. Of note, MTX is part of the maintenance regimen for the CALBG 9710 protocol [3] and the PETHEMA protocol [4] but there was no significant association. Moreover, only 55% of patients with such complaints were referred to psychiatry or neurology and only 13% of those patients had a full neurocognitive evaluation. Although chronic neurological AEs in APL patients has not been reported [5], these findings warrant closer monitoring of neurological AEs and increasing awareness of these deficits.

In summary, patients receiving conventional therapies for APL experienced a range of cardiac and neurologic AEs following diagnosis and treatment. In the current analysis, we identified potential risk factors for development of those AEs, which may be areas for future study. As the focus in treatment of APL moves toward improving survivorship, it will be important to consider cardiac and neurological care as a part of survivorship guidelines.

Conflict of interest

Amir T. Fathi has served on an advisory board for *Seattle Genetics*. The other authors report no relevant conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lrr.2018.05.001.

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