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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 neurological 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 transplantation for myelodysplastic syndrome.

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%)

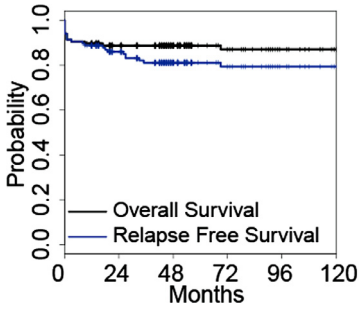

Fig. 1. Overall survival (OS) and relapse free survival (RFS) in APL patients.
Kaplan–Meier curve of OS and RFS demonstrates survival rates consistent with modern treatment strategies.

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)

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