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Letters to the Editor

# Prevention of Early Death in Very Elderly Acute Promyelocytic Leukemia Patients Using Lower Induction Doses of All-trans Retinoic Acid

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**To the editor.**

With the introduction of differentiating agents all-trans retinoic acid (ATRA) and arsenic trioxide (ATO), acute promyelocytic leukemia (APL) has evolved from being one of the most life-threatening diseases to becoming the most curable subtype of adult acute myeloid leukemia.[1] However, despite this advancement, early deaths of 20 to 30% within the first 30 days are the most frequent and frustrating cause of treatment failure in this disease.[2,3,4] Amongst elderly patients, this remains an even more critical issue with an early death rate as high as 50%.[3,5] Unfortunately, limited data are available on the elderly population due to frequent exclusion from clinical trials, given that age and associated comorbidities are a prominent negative risk factor. Differentiation Syndrome (DS) plays a significant role in causing morbidity and mortality amongst elderly APL patients.[6,7] This is due to side effects, such as peripheral edema, hypotension, pulmonary edema, pleural effusion, and/or renal dysfunction, which impact patients with comorbidities and decreased reserve to a much greater degree. Currently, the standard-of-care for APL therapy is to give ATRA at 45 mg/m$^2$ to adult patients; however, low-dose ATRA (25 mg/m$^2$ or less) has been offered in adults and children with APL in prior studies and shown to reduce the occurrence of ATRA-associated side effects.[8,9] It is also interesting to note that pharmacokinetic studies comparing 25 mg/m$^2$ of ATRA to 45 mg/m$^2$ in adult APL patients have shown comparable peak concentrations and mean area under the curve.[10] Based on our extensive experience with reducing induction deaths in two multicenter trials and the high morbidity and mortality associated with standard dose ATRA, we proposed that lower doses of ATRA in very elderly APL patients reduce complications and result in a lower rate of early deaths.[11,12]

A retrospective analysis was conducted with institutional review board (IRB) approval of all elderly APL patients treated between 2017 and 2023 at Georgia Cancer Center in Augusta, GA. Screening was performed for all APL patients aged 70 years or older. Nine patients were identified and are summarized (**Table 1**). The patient population was between 70 and 88 years old, with a median age of 75 years. One female patient was classified as high risk and presented with white blood cell (WBC) of 31.7 x 10$^9$/L, while the rest were considered low risk with WBC <10 x 10$^9$/L. Due to age and significant comorbidities, all nine received dose-reduced ATRA (equal to or less than 25 mg/m$^2$/day). ATRA was started as soon as APL was suspected, and patients were treated according to a simplified algorithm that emphasized the identification and prevention of disease and treatment of associated complications.[11,12]

Prednisone at 0.5 mg/kg was started at diagnosis in all low-risk patients except one, and dexamethasone 10 mg twice a day was started in the one high-risk patient per previously published protocols.[13] ATO was added after 10-14 days of therapy at a dose of 0.15mg/kg daily or less if the patient was stable and deemed able to tolerate it. Cytoreductive agents, cytarabine and hydroxyurea, were used for hyperleukocytosis. Weights were obtained daily, and aggressive diuresis was performed to maintain patients at baseline weight. At the first sign of DS, ATRA was held, and the corticosteroid dose increased.

One early death was observed in the group. The patient was an 81-year-old Caucasian male with low-risk APL who elected to halt treatment and pursue hospice on day 17 of therapy and passed away on day 18. He was diagnosed with moderate DS on day 15 and reported having significant abdominal pain, dyspnea, and fever. He had several comorbidities, including coronary artery disease status-post 3-vessel coronary artery bypass graft, hypertension, and type 2 diabetes

**Table 1**. Early death outcomes of very elderly APL patients.

| Age | APL Risk | Initial ATRA dose | Received PPX steroids | Grade of DS severity | Days ATRA held | Peak WBC (x$10^9$/L) | Comorbid Conditions | Early Death |
|---|---|---|---|---|---|---|---|---|
| 81 | Low | 10 mg/m$^2$ | Yes | Moderate | 10 | 45.7 | CAD s/p 3 vessel CABG, HTN, T2DM, and tobacco abuse | Yes |
| 75 | Low | 6 mg/m$^2$ | Yes | Indeterminate | 8 | 12.2 | CVA, T2DM, subdural hematoma s/p craniotomy, breast cancer s/p mastectomy with adjuvant RT, and HTN, CAD, HLD, GERD | No |
| 88 | Low | 2.5 mg/m$^2$ | Yes | Indeterminate | 8 | 7.2 | Aortic stenosis s/p TAVR, HLD, GERD, HT-H, and mild dementia | No |
| 70 | High | 9 mg/m$^2$ | Yes | Severe | 15 | 38.5 | Paroxysmal AFib, SSS s/p ICD, HFpEF, TIA, OSA, GERD, HT-H, and HTN | No |
| 86 | Low | 17 mg/m$^2$ | Yes | Indeterminate | 4 | 14.7 | HTN, macular degeneration, gout | No |
| 70 | Low | 25 mg/m$^2$ | Yes | Indeterminate | 5 | 11.3 | Paroxysmal AFib, peripheral vascular disease s/p angioplasty, CVA, and HTN | No |
| 75 | Low | 9.5 mg/m$^2$ | Yes | Moderate | 6 | 22.2 | T2DM, HTN, colon cancer s/p resection, and prostate cancer s/p external beam radiation therapy | No |
| 70 | Low | 5.3 mg/m$^2$ | No | Moderate | 12 | 50.6 | Long QT syndrome and recurrent Torsades de pointes s/p ICD, NICM, HT-H, anxiety, MDD, insomnia, HLD, HTN, and pAFib | No |
| 76 | Low | 25 mg/m$^2$ | Yes | Indeterminate | 4 | 60.8 | HTN, T2DM, ovarian cancer s/p chemotherapy and TAH with BSO | No |

Abbreviations: CAD: coronary artery disease; CABG: coronary artery bypass graft; HTN: hypertension; T2DM: type 2 diabetes mellitus; CVA: cerebrovascular accident; RT: radiation therapy; HLD: hyperlipidemia; GERD: gastroesophageal reflux disease; TAVR: transcatheter aortic valve replacement; AFib: atrial fibrillation; SSS: sick sinus syndrome; ICD: implantable cardioverter-defibrillator; HFpEF: heart failure with preserved ejection fraction; TIA: transient ischemic attack; OSA: obstructive sleep apnea; MDD: major depressive disorder; TAH: transabdominal hysterectomy; BSO: bilateral salpingo-oophorectomy; HT-H: hypothyroidism; NICM: non-ischemic cardiomyopathy; pAFib: paroxysmal atrial fibrillation; APL: acute promyelocytic leukemia; ATRA: all-trans retinoic acid; PPX; prophylactic; WBC: white blood cell; N/A: not applicable.

mellitus. Overall, the early death rate was noted to be 1/9 (11%) in this group, which is significantly lower than what has been reported in existing literature.[3,5] DS was noted to play a significant role in the care of all nine elderly APL patients. The severity of DS was graded according to the model proposed by the Programa de Estudio y Tratamiento de las Hemopatías Malignas (PETHEMA) group (**Table 1**).[14,15] Diagnosis of DS was made according to the presence of dyspnea, unexplained fever, weight gain greater than 5 kg, unexplained hypotension, acute renal failure, and a chest radiograph demonstrating pulmonary infiltrates or pleuropericardial effusion.

Patients with alternative explanations for the above signs or symptoms, such as septic shock, pneumonia, or heart failure, were not considered to have DS. If four or more of the above signs or symptoms were present, the patient was diagnosed as having severe DS. If two or three of the above signs or symptoms were present, the patient was classified as having moderate DS. If one of the above signs or symptoms were present with no other alternative explanation, the patient was classified as indeterminate DS. ATRA was held for different lengths of time throughout each patient's hospitalization due to DS. This was seen despite the use of prophylactic steroids in eight out of the nine patients (**Table 1**). Several patients had their ATRA dose reduced further due to concern for recurrence of DS during induction therapy. Out of the nine patients treated, one was noted to have severe DS. This patient had an initial ATRA dose of 9 mg/m$^2$/day and required multiple dose reductions. ATRA was held for a total of 15 days due to DS in this patient. Of note, the patient also required admission to the Intensive Care Unit, with a length of stay of 2 days.

Maximum WBC count during induction therapy has been shown to correlate with both DS and early death, so this was also explored further.[14] The patients with moderate and severe DS had a WBC count that ranged between 22.2 and 50.6 x $10^9$/L. It was also interesting that the one early death was noted in an 81-year-old patient with moderate DS with a maximum WBC count of 45.7 x $10^9$/L. These findings support what previous studies have shown regarding the correlation between maximum WBC and DS as well as early death.[16] ATRA at a reduced dose was also given for consolidation (**Table 2**). Five out of the nine patients were able to receive further consolidation therapy, and all of them achieved complete hematologic and molecular remission. One patient was not a candidate for consolidation due to performance status and was later noted to have relapsed disease. Of the five patients who received induction and consolidation, one patient relapsed and continued therapy for several years.

**Table 2**. Long-Term Outcomes Using ATRA at Reduced Dose.

| Age | Risk | Induction ATRA Dose Range | Induction ATO Given | Consolidation ATRA Dose | Complete Remission | Relapse | Time of Death (days from APL diagnosis) | Cause of Death |
|---|---|---|---|---|---|---|---|---|
| 81 | Low | 10 mg/m$^2$ | No | N/A | No | N/A | 18 | APL - hospice |
| 75 | Low | 6 - 12mg/m$^2$ | No | 11.7mg/m$^2$ | Yes | No | 506 | Intraparenchymal hemorrhage |
| 88 | Low | 2.55 - 10 mg/m$^2$ | Yes | 10 mg/m$^2$ | Yes | No | 254 | Acute myocardial infarction |
| 70 | High | 2.2 - 9 mg/m$^2$ | No | N/A | Yes | Yes | 444 | Relapsed APL - hospice |
| 86 | Low | 17 mg/m$^2$ | No | N/A | No | No | 44 | APL - hospice |
| 70 | Low | 9.5 - 24 mg/m$^2$ | Yes | 25 mg/m$^2$ | Yes | No | Alive | N/A |
| 75 | Low | 4.6 - 9.5 mg/m$^2$ | Yes | No (left AMA) | No (left AMA) | N/A | 524 | Unknown |
| 70 | Low | 5.3 - 10.5 mg/m$^2$ | No | 10.7 mg/m$^2$ | Yes | Yes | 1125 | PNA/AHRF - hospice |
| 76 | Low | 25 mg/m$^2$ | Yes | 25 mg/m$^2$ | Yes | No | 300 | Metastatic ovarian cancer - hospice |

Abbreviations: ATRA: all-trans retinoic acid; APL: acute promyelocytic leukemia; PNA: pneumonia; AHRF: acute hypoxic respiratory failure; N/A: not applicable; AMA: against medical advice; ATO: arsenic trioxide.

Early death amongst APL patients, especially the elderly, remains a critical issue despite significant advances in therapy over the past 20 years. Clinical trials often exclude elderly patients due to age being a negative risk factor, so it is unclear what the most appropriate strategy should be regarding induction therapy. As patients age, the prevalence of other comorbidities increases, and that results in a greater chance of complications with induction therapy, suggesting that a more individualized approach may be necessary. From our earlier experiences, we learned that elderly patients tolerate standard doses of ATRA poorly, with increased deaths due to DS, and so subsequently decreased the doses, which showed improved outcomes.[11,12] One of the areas of focus we looked at was how elderly APL patients responded to lower doses of ATRA compared to the standard regimen of 45 mg/m$^2$. Interestingly, only one early death was noted, and this patient decided to pursue hospice due to negative effects from DS. It is also important to note that all the patients were affected by DS, despite receiving lower doses of ATRA as well as prophylactic steroids. These findings suggest that DS may be playing a greater role in influencing early death rates amongst elderly patients than previously believed. One of the ways that the severity of DS can be targeted and early death rates decreased is by administering lower doses of ATRA during induction therapy and withholding the drug at the first sign of DS. We suggest 25 mg/m$^2$ of ATRA in patients above 70 years of age, and a further decrease to 10 mg/m$^2$ in the very elderly with significant comorbidities. Single agent ATRA during induction and adding ATO later in induction, if there is no evidence of DS or leukocytosis, or only during consolidation, is an approach we used. We believe that this area needs to be explored further and could be crucial to improving survival amongst elderly APL patients.

Mark Dalgetty[1,2], Sruthi Dontu[2], Chandini Kannan[2], Amany Keruakous[1], Locke Bryan[1], Vamsi Kota[1] and Anand Jillella[1].

[1] Georgia Cancer Center at Augusta University, Augusta, GA, USA.
[2] Medical College of Georgia at Augusta University, Augusta, GA, USA.

**Competing interests:** The authors declare no conflict of Interest.

Correspondence to: Anand Jillella, MD. Georgia Cancer Center at Augusta University, 1120 15th St, CN 5335, Augusta, GA 30912, USA. Tel: 706-951-5144. E-mail: ajillella@augusta.edu

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