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Review

The global problem of early deaths in acute promyelocytic leukemia: A strategy to decrease induction mortality in the most curable leukemia



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ABSTRACT

Acute promyelocytic leukemia (APL) is a hyper-acute illness and presents with profound cytopenias in most patients and disseminated intravascular coagulation (DIC). Excellent treatment options are now available with drugs such as all-trans retinoic acid (ATRA), arsenic trioxide (ATO), anthracyclines and cytarabine. The outcome in APL has improved tremendously in the last 50 years due to better understanding of the disease, development of effective targeted agents and improvement in supportive care. Carefully selected groups of patients treated in large multi-center trials on a protocol and in experienced centers have shown survival rates in excess of 85%. However population data and other studies show that approximately 30% of patients die during induction. This is an Institutional, national and global problem and remains a pressing and frustrating challenge in APL.

While most APL experts are aware of the high rate of early deaths (ED), such awareness is not typically present among general hematologists and oncologists. Our area of focus over the last 7 years has been the reduction of ED in both academic and community centers; as a result we have acquired substantial experience in APL induction. Two centers have implemented population-wide prospective trials; Brazil and Georgia/South Carolina, USA with improvement in the ED rate. Both centers used standardized guidelines along with consultative support and sharing of expertise which proved effective and helped to decrease ED.

Induction mortality in APL is 30% or greater. We believe ED is largely preventable and population-wide survival can be improved. An effective strategy is to utilize a set of simplified treatment guidelines coupled with support from a group of experts during induction. Treating oncologists in both academic and community hospitals should receive aggressive education about ED and be encouraged to seek advice from a core group of established APL experts. This model could be implemented nationally to improve population-wide survival in this most curable leukemia.

1. Introduction

Acute promyelocytic leukemia (APL) is a rare but curable leukemia characterized by translocation t(15; 17) that leads to the production of the onco-protein PML-RAR alpha. Patients generally have a characteristic presentation with cytopenias and disseminated intravascular coagulation (DIC). Early deaths have been described as death within 30 days of diagnosis. Large, multi-center clinical trials have reported an ED rate of 3 to 10% in patients treated with all-trans retinoic acid (tretinoin, ATRA), anthracyclines, and arsenic trioxide (ATO) [1–5]. However, this might be a gross under-estimate of deaths during induction given that most patients entered in multi center trials are highly selected and treated on protocol and managed at experienced centers. In patients not eligible or excluded from trials, the death rate has been reported to be approximately 20% [6]. In large population based

analyses and among all patients treated in single institutions the rate of induction mortality is higher and can range from 9.6 to 61.5% (Table 1) [7–21]. These data show that almost 1 in 3 patients diagnosed with APL dies within the first month. A large challenge is the scant availability of population-wide data from developed countries and near absence of data from emerging and developing nations. Population based reports from the USA, Sweden and Canada appear to show no improvement in early deaths in the past two decades despite the use of currently available modern drugs. These observations warrant a clear need to change the approach in newly diagnosed patients in order to improve population-wide survival. Disappointingly, few active programs exist to address the prevention of early mortality in large populations.

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Table 1
Early deaths – population wide, multiple centers and single centers.

Study	Total patients	Patients died	Mortality rate %
Brazil [7]	134	43	32
Sweden [9]	105	30	29
SEER, USA [10]	1400	238	17 (24 in age > 55)
Canada [17]	399	87	22
France [21]	399	39	9.6
Turkey [8]	49	20	40
Tunisia [12]	51	7	14
Stanford, USA [13]	70	19	26
Greece [14]	95	14	15
Augusta, GA, USA [16]	19	7	37
Japan [15]	32	7	21.3
Pakistan [18]	26	16	61.5
Emory, USA [20]	75	19	25

1.1. National/population wide data

The first group to identify ED as a problem was Jacomo et al. from Brazil [7]. Among 134 patients treated from 2003 to 2006 with anthracycline/ATRA based regimens at 12 centers, there were 43 deaths (32%). Since patients were treated in 12 different referral centers across the country these findings were felt to be a broader representation of the problem. A delay in patient transfer to a specialty center and non-aggressive supportive care during induction resulted in inordinately high ED and was a major impediment to survival. Notably, there was no difference in ED between the 12 referral centers. The authors also concluded that the death rate of 32% in the Brazilian study reflected patients treated in referral centers; if patients treated in non-referral centers were included the number would be higher. This analysis showed that timely diagnosis and better supportive care could result in improved outcomes in developing countries and led to the development of the International Consortium on APL (IC-APL).

The concept of ED being a problem in only developing countries came under scrutiny when Lehman et al. published Swedish registry data in 2011 [9]. All APL patients diagnosed between 1997 and 2006 in the population-based adult acute leukemia registry were included in the study. Out of a total of 105 patients, 30 died (29%) within 30 days and 23 (77%) of the early deaths took place within 7 days of diagnosis. The survival at 6 years in the Swedish population-based retrospective analysis was 62%, which pales in comparison to the 90% seen in large multicenter trials. Interestingly, the study showed there was a difference in the rate of ED between centers, with 22% ED in University hospitals and 52% in intermediate and small hospitals. This was the first national analysis of all APL diagnoses with no exclusions suggesting the outcome in the “Real World” as opposed to a controlled clinical trial environment. Since health-care is quite sophisticated in Sweden, the authors concluded this to be the approximate death rate in developed countries.

While high early mortality was suspected in the US, definite evidence was established only recently by a well-designed epidemiologic study conducted by Park et al. utilizing the Surveillance, Epidemiology and End Results (SEER) program database. In the largest population-based analysis, a total of 1400 patients diagnosed with APL between 1992 and 2007 showed an ED rate of 17.3% overall and 24% among patients aged > 55 years. These results might be an underestimate due to flaws in the SEER reporting system and that the actual death rate may be higher. While the general bias is to attribute the deaths to rural and inexperienced centers, there was no difference in this analysis; although there was some suggestion of more deaths from hemorrhage in non-specialized and inexperienced institutions. Survival improved to 55.6% between 1992 and 1995 (after the introduction of ATRA), 66% from 1996 to 2001, and 70.5% from 2002 to 2007. Survival decreased sharply in the first 2 months but declined at a much lower rate after 2 months [10]. Investigators from MD Anderson analyzed SEER data

from 9 districts and compared it to their Institutional experience. Between 1991 and 1999 and 2000–2008 there was no significant improvement in 1 year survival [11].

The Canadian Cancer Registry (CCR) data base included 399 patients with APL from 1993 to 2007 with an ED rate of 21.8%. Neither ED nor OS improved over time in the general population when different time periods were analyzed [17]. Interestingly in the Canadian study, ED information was collected from 5 referral centers on 131 patients from 1999 to 2010 with 14.6% early deaths. When different time periods were compared, ED in referral centers improved from 18% in 1999 to 2004 to 11% from 2005 to 2010. Despite having a sophisticated healthcare system as well as the universal availability of health-care and access to drugs, the ED rate in Canada was no better than in other countries.

1.2. Institutional studies

There are several reports from single centers or a small group of centers that show an unusually high mortality rate. A study from Hacettepe and Ondukuz Universities (Turkey) reported 20 early deaths among 49 patients treated between 2003 and 2008 (40.8%) [8]. McClellan et al. analyzed data from patients treated at Stanford University from 1997 to 2009 [13]. Among 70 patients treated with induction therapy, 27% died during the first 30 days and 19% in the first week, making ED the most common cause of treatment failure. In a retrospective analysis, investigators from the Agha Khan University, a tertiary care center in Pakistan, treated 26 patients between 2007 and 2008; 16 of the 26 (61.5%) patients suffered ED [18]. The All India Institute of Medicine, a tertiary care center in India, treated 33 patients from 1997 to 2007 and reported an induction mortality rate of 18% [19]. We also analyzed ED in two large centers in the state of Georgia, US and reported a rate of 27% [20]. Of 51 patients treated at the Hematology Department of the Aziza Othmana tertiary care hospital in Tunisia, 7 patients (14%) experienced early death [12]. In Greece, among 91 patients diagnosed in 6 tertiary centers, the ED rate was 14.9% [14]. In a French study that addressed ED in all patients diagnosed with APL and referred to 17 centers from 2006 to 2011, a total of 399 patients were identified. An effort was made to identify all APL patients whether treated on or off a trial; 68.7% of patients were included in a trial. The overall ED in the French trial was 9.6% with 2.5% in patients on trial and 17% in non-trial patients. While this finding was from large and experienced centers, outcomes in smaller French centers and population-wide survival are not known. Their lower mortality rate in this study was attributed to rapid diagnosis and initiation of ATRA treatment with placement on a protocol and rigorous adherence to supportive care [21] Table 2.

1.3. Causes of early death

In multi-center studies that specifically assessed deaths during induction, the most frequent causes of death were identified as bleeding, differentiation syndrome (DS), infection and multi-organ failure Table 3.

Table 2
Practice points.

- Induction mortality in clinical trials is 3–10%.
- There are a few published registry reports from developed countries and none from developing countries.
- Induction mortality in the general population is approximately 30%.
- Induction mortality has not improved in the last two decades.
- Early death among APL patients exists in experienced and inexperienced centers.
- Early death is a global problem in developed, emerging and developing nations.
- Practicing hematologists and oncologists may not be aware of the gravity of this problem.

Table 3
Practice points - causes and risk factors of early death.

CAUSES
Hemorrhage
Differentiation syndrome
Infection
Multi-organ failure
RISK FACTORS
Advanced age
High risk disease
Poor performance status
Infection/fever
Obesity
Conflicting data exists for increased creatinine, gender, fibrinogen level, early versus delayed ATRA administration, treatment in an experienced vs inexperienced center.

1.4. Hemorrhage

The PETHEMA group reported on 732 patients treated with ATRA and idarubicin in 2 consecutive studies (LPA 96 and LPA 99) with an ED rate of 9% [22]. 56% of the deaths were caused by hemorrhage with the brain being the most common site (65%) followed by the lung 32% [23]. Similarly Japanese and German studies reported hemorrhage as the cause of death in 69% and 64%, with a majority of the deaths occurring in the first week [24–26]. A single Institution study from Stanford that assessed ED and its causes, showed that 54% of patients died from hemorrhage [13]. The Brazilian 12 center study showed 66% of the deaths were from bleeding. In another small study of 26 patients there were 16 deaths, 43% of which were caused by bleeding [18]. The Swedish study, the only population-wide registry, attributed 41% of the deaths to hemorrhage [9]. In a study by He et al. 26/128 patients had ED and 24 of these (92%) were caused by intracranial bleeding. The deaths were attributed to weekend admissions, delay in diagnosis, and initiation of APL directed therapy [27]. In the Brazilian IC-APL trial meant to decrease induction mortality, 13 of 27 deaths were from bleeding (48%). Of the 17 patients in this trial that were deemed ineligible, 7 deaths were from bleeding (41%). Hemorrhage by far is the most common cause of early deaths during induction [28].

1.5. Differentiation syndrome

In the PETHEMA LPA 96 and 99 trials, 10 of the 66 induction deaths (15%) were from differentiation syndrome (DS). In the LPA 96 trial, patients with a WBC > 5 × 10⁹/L and in the LPA 99 trial, all patients were placed on prophylactic prednisone. This may have decreased deaths from DS [22,23]. In the IC-APL Latin American study, 18.5% of the induction deaths were due to DS [28]. In a small study of 26 patients, all 7 who developed differentiation syndrome died (43%) [18]. However, in the most recently concluded and published APL trials, the Australasian Study (APML4) reported no deaths from DS, the Italian-German APL0406 trial reported 2 of the 4 deaths were from DS, and the UK National Cancer Research Institute Acute Myeloid Leukemia Working Group AML 17 trial did not elaborate on causes of death. The first two of these trials used prophylactic steroids in all patients but the AML 17 trial did not [4,5,29].

1.6. Infection

The study by Jacomo et al., cited infection as a cause of ED in 6/43 (14%) of the patients [7]. In other studies that addressed causes of death, infection accounted for 12% to 27% [18,22,28]. In the LPA 96 and LPA 99 trials, 17 of 66 (25%) induction deaths were caused by infection and the median time to death in this group was 21 days (range 3–39 days) from the beginning of therapy [23].

1.7. Multi-organ failure

Multi-organ failure is listed as a cause of death in some reports. The reasons for multi-organ failure are not clear but it most likely results from infection, DS or both.

2. Risk factors for early deaths

From studies that have elaborated on the causes of death, several factors have been studied by univariate or multi-variate analysis. Certain risk factors have been associated with ED.

2.1. Age

Advanced age is consistently a risk for ED. In two recent GIMEMA-GAAMLSG (APL0406 trial) and the Australasian Leukemia Group multicenter trial (APML4), the median age was 44.6 to 46.6 and 44 years respectively [4,5]. This median age range is typical in most clinical trials; the median ages in the LPA 96, LPA99 and AML17 studies were 40, 39 and 47 years respectively. In the Latin American IC-APL trial patient age range was 15–73 with a median age of 34; this is much lower than that seen in the general population. The Swedish Registry data, the most comprehensive population data had a median age of 54 years and an induction mortality in patients > 60 of 60% [9]. A study by Jillella et al. included all comers with no exclusion and the median age was 52 [30]. The US SEER data showed a mortality rate of 24% in patients above 55 years of age but details in patients above 60 and 70 years were not available. The median age in this study was 44 which raises the question of whether all APL patients were captured by the SEER database [10]. Analysis by the MD Anderson group showed the relative survival at 1 year in patients above 60 years of age was 38%, suggesting a very high failure rate in the first year [11]. Canadian Registry data showed a mortality of 35.5% in patients above 50 years but the study fails to report death rate in patients above 60 and 70 years even though most publications defined “elderly” as patients above 60 years old [17]. In the LPA 96 and 99 trials of 127 patients above age 60, 18 APL patients were ineligible due to poor performance status or death before starting treatment and for other reasons. Of the 104 evaluable patients there were 17 deaths 16.3%. The 8 patients who died before starting treatment and the outcome in the 10 patients excluded for poor performance status were not reported nor included in the deaths. Clearly there were more deaths in all APL patients > 60 in this study confirming that death rate is significantly higher in elderly patients [31]. In a German Cooperative Group (AMLCG) registry, 91 patients above the age of 60 were identified (median age 67). 75% were treated on a trial and 25% were non-eligible. The ED rate was 48% in the non-eligible and 19% in the study patients. Age above 70 in the German trial was associated with an inferior outcome [32]. The study by Ferrara et al. analyzed 34 patients above the age of 60, 23 were treated on trial and 11 off trial due to poor performance status or comorbid conditions. The induction mortality rate was 32% with the knowledge that at least two thirds of patients were fit enough to be treated on trial [33]. The Stanford review also showed that patients who suffered ED had a median age of 57 compared to 47 in non-ED patients [13].

2.2. High risk patients

Several individual and registry studies have shown a high white blood cell count to be a contributor to ED [9,12,13,14,18,27]. In the Jacomo study from 12 Brazilian centers, early mortality in high risk patients was unusually high at 75%, prompting the author to conclude the need for a different strategy both for induction and consolidation in this group [7]. In a large cohort of 732 patients from the PETHEMA study, induction therapy was unsuccessful in 66 patients, all of them due to early death. A high white cell count and increased circulating

blasts were risk factors for early deaths [23]. In an analysis by Kelaidi et al. of high risk patients treated in multiple trials, the mortality rate was 5–42% [34].

2.3. Poor performance status

In the Swedish Registry study, patients with a WHO performance status (PS) of III - IV had a mortality rate of 78% whereas PS of I was associated with an ED of 7.1%. Interestingly, 43% of patients older than 60 years had a poorer PS (III-IV) compared to 10% of patients below 60 years of age. Also in the same study younger patients aged 40–59 with a PS of III-IV had an ED rate of 70%, showing that PS is closely associated with early deaths [9]. In the PETHEMA experience an ECOG score of II-III was associated with more frequent induction deaths [23].

2.4. Other risk factors

Other risk factors for ED have been suggested including increased creatinine, gender, early versus delayed administration of ATRA and fibrinogen levels, but have not been consistently supported in studies [9,13,14,21,23,25,35,36,37]. The presence of infection, fever at diagnosis and obesity have been found to be risk factors for ED [14,23,38]. At least 2 studies suggest that treatment in larger and more experienced centers decreases induction mortality but there are also reports of experienced centers with high ED rates [9,17]. The US SEER data showed no difference in mortality between rural and urban areas [10].

3. Are APL early deaths preventable?

While it is now recognized that early deaths are the most frequent cause of treatment failure, there are few population or national based programs in place to decrease induction mortality. However the outcomes of studies conducted in Brazil and in Georgia/South Carolina (USA), suggest that a vast majority of the deaths are preventable.

3.1. Brazilian experience

Given the high induction and consolidation deaths rates of 42%, the IC APL (International Consortium in APL) trial was initiated in Brazil, Mexico, Chile and Uruguay [7]. Centers were chosen based on the availability of drugs, appropriate supportive care, diagnostic tests and the ability to participate in web based conferences. A program of education to create awareness of APL was undertaken prior to initiation of the study. Treatment guidelines were formulated to suit local conditions and were part of the protocol specifically focusing on transfusion support to prevent bleeding and meticulous monitoring of weight to prevent DS [39]. Additionally, frequent virtual meetings were held to discuss new patients, patient progress, and to share expertise. When possible, international experts participated and face to face meetings of all participants were held every 6 months. A total of 215 patients were evaluated of whom 15 were not confirmed as having APL and were excluded. 183 patients were enrolled in the trial with 27 deaths (15%). However, 17 patients with APL were ineligible of whom 7 died. This was a remarkable improvement in early deaths compared to the historical mortality rate of 32% [28].

3.2. Georgia, South Carolina (USA) experience

At Georgia Regents University (GRU) Medical Center, Augusta, Georgia, USA, from July 2005 to June 2009, 19 APL patients were treated with 7 (37%) deaths prompting a critical review of our treatment processes. After a thorough assessment, a simple 2 page treatment algorithm was developed highlighting the most important methods to prevent complications leading to ED (Appendix A). The algorithm allows for rapid diagnosis, expeditious implementation of a treatment plan and rigorous adhesion to supportive care. A mechanism was

created to quickly transfer the patient to GRU if requested by the referring physician and the program was implemented in 2010 with IRB approval. GRU functions as a tertiary referral center and a network of leukemia treating hospitals was established in Georgia, South Carolina and neighboring states. Aggressive outreach effort was made by visiting most of the leukemia treatment hospitals to create awareness of the concept and educate treating physicians in the community about ED in APL. Expert and treating physician communication via phone and email was established very early and was maintained until the completion of induction. From November 2010 to June 2015, a total of 106 patients were treated or co-managed by the team. There were no exclusion criteria although 3 Jehovah's Witness patients were excluded for refusing transfusion support. 40 patients were managed at large leukemia treatment centers and 66 were managed in the community at 18 practices spread across Georgia, South Carolina and neighboring states. Median age was 52 years (range 21–87 years) and 53% were males. There were 7 deaths (6.6%) five of which were in patients older than 60 years and 3 being patients above 70 years. Deaths occurred in both academic (2/40, 5%) and community (5/66, 7%) centers. Our experience shows that a streamlined treatment algorithm along with consultation from experts can result in better outcomes [30].

4. Discussion

The problem of early deaths in APL has come into the limelight only in the last decade with reports from Brazil and Sweden in 2007 and 2009. Subsequently, there have been at least 20 publications from national registries, multi-center analysis and single Institution studies. On the positive side, there appears to be an increase in awareness yet further improvements in understanding are needed among treating oncologists regarding the most frequent cause of treatment failure. With the availability of highly effective drugs, the DFS and OS have improved; however, induction mortality remains unchanged in the last 2 decades. ED in most studies has been described as death within 30 days of diagnosis. This may not be an accurate end-point and should possibly be extended until the completion of induction, which could extend beyond 30 days [40].

An explanation for the high rate of ED is the rarity of APL coupled with the fact that a majority of APL patients are treated outside of clinical trials and in smaller inexperienced centers. There are approximately 1500 cases of APL per year in the US, and 13,000 practicing hematologists/oncologists averaging 1 patient for every 10 oncologists per year [41,42]. APL is an orphan disease yet with very effective interventions. Experience with its management may not be higher even in large tertiary centers. A recent retrospective review reported that 204 patients were treated over a period of 18 years at Rambam Medical Center, Israel; Memorial Sloan Kettering Cancer Center, New York; Northwestern University, Chicago and Cook County Hospital, Chicago which amounts to fewer than 3 patients per year per center [35]. The MD Anderson cancer center treated 242 patients over a period of 29 years averaging 8.3 patients per year [11]. Given the low incidence of the disease, treating centers see few patients per year and treating hematologists even fewer. In our study of 106 patients 38% were treated in large leukemia treatment centers and the remainder at 18 hospitals in Georgia, South Carolina and neighboring states over a 4 year period [30]. Contributing factors to the ED rate are the acute, complex, and protean manifestations of the disease along with the lack of experience among treating oncologists in anticipating and managing complications of the drugs. Although data from some experienced institutions show a mortality consistent with the < 10% observed in clinical trials, the rate is higher in several tertiary centers [10,13,20,35,43].

Extensive literature and elaborate position papers have been written on APL treatment, but for the oncologist who may treat an APL patient sporadically, this may not be practical [44,45]. Since it is vital to act with speed and precision at initial presentation, simplified and

prioritized guidelines in the form of a checklist would be highly useful. Two prospective studies showed that the use of standardized guidelines specifically targeted at decreasing bleeding, DS and infections helped to decrease early mortality [28,30,39]. Also noteworthy, is that patients treated on a trial with prescribed guidelines on supportive care do extremely well.

Early deaths due to hemorrhage are the hallmark of APL. Even though DIC is rapidly corrected after treatment begins, bleeding risk needs to be closely monitored even after the initiation of treatment [44]. The GIMEMA group published their experience in the management of APL and showed that all patients were managed under a uniform protocol across all treatment centers. The transfusion requirements and anti-hemorrhagic treatments were aggressively implemented; these guidelines were followed even before the advent of ATRA [46]. The MD Anderson group reported on the use of ATRA and ATO in low and intermediate risk APL while strictly adhering to supportive care guidelines with platelets maintained above 30,000, fibrinogen > 150 and INR < 1.5 [47]. Data from Stanford showed that despite adequate platelet support, fibrinogen and INR were not maintained in the recommended range hence the high death rate. Lack of treatment algorithms and strict adherence to the published regimens is most likely absent in settings outside a clinical trial and in smaller institutions with rare APL cases that lack a standardized operating procedure.

Focus should be on preventing complications such as DS and infection that account for 30% of the deaths [48,49]. Recent paradigm shifting studies, the PETHEMA LPA 96 and LPA 99, GIMEMA-GA-AMLSG (APL0406 trial) and Australasian Leukemia Group multicenter trial (APML4) used prophylactic doses of prednisone or dexamethasone to prevent DS and used treatment doses for symptoms suggestive of established DS [2,4,5]. Keeping the patient euvoemic by aggressive diuresis and preventing weight gain has helped decrease deaths from DS in the experience of our group, the PETHEMA group and others [30,39,49]. Multi-organ failure is probably a result of infections or more likely from differentiation syndrome or a combination. Using prophylactic antibiotics as the usual practice in acute leukemia and aggressively treating infections should be the general standard of care.

Older patients are the most vulnerable population with death rates in excess of 50%. The goal in older patients should be to get them through induction and achieve CR since they generally present with low risk disease and are less likely to relapse after achieving CR. While many centers have analyzed clinical trial data and the causes of death in older patients, established effective strategies to decrease deaths in this patient population are limited. The use of fewer and less intense doses of anthracyclines and possibly using non-cytotoxic approaches such as ATRA and ATO may be successful [31,50–54]. Ferrara et al. in a small series of patients with a median age of 70 years treated 11 patients with single agent ATRA at 45 mg/M² and achieved CR of 54% with 5 deaths [30]. Since older patients have co-morbid conditions and a poor PS, myelo-suppressive chemotherapy is poorly tolerated. Single agent ATRA or ATO or a combination at lower doses might be an option but this needs to be systematically studied. Kota et al. treated 47 patients over 60 years of age of whom 43 were treated with a combination of ATRA and ATO. A majority of these patients received reduced doses of ATRA and ATO with 6 deaths (13.3%) [55]. Alternatively, single agent ATO has been used extensively for induction with a high CR rate. In one study, there were 5 patients above 55 and in a second study the age range was 11 to 71 years even though the study fails to mention the number of patients > 60 [56,57]. Zhang et al. in a cohort of 33 Chinese patients used single agent ATO during induction at 0.16 mg/Kg (capped at 10 mg); the dose was decreased further in patients with co-morbid conditions or decreased or held in the event of leukocytosis or differentiation syndrome. The early death rate in this small series was 12% which is an improvement [58]. Single agent ATO reduced or capped at 10 mg maybe suitable in patients who are elderly, frail or have co-morbid conditions.

Table 4
Practice points to decrease induction deaths.

- Creating awareness among treating oncologists
- Development of standardized and simplified guidelines for diagnosis and treatment
- Expedited implementation of treatment plan
- Start ATRA at first suspicion of APL
- Prevention of hemorrhage with aggressive transfusion support
- Prophylactic doses of steroids for prevention and treatment doses for established cases of DS. Maintaining a euvoemic state.
- Prophylactic antibiotic use.
- Early cytotoxic chemotherapy in patients with high white counts
- The management of older patients is unclear. Single agent and dose reduced ATO or ATRA or both are options but have to be systematically studied.
- Having centralized expertise and seeking early advice maybe useful for providers and centers with limited experience.

Since APL is a rare disease having a resource with experience in providing supportive care and managing treatment complications of the drugs appears to improve the outcome. Two prospective studies have shown this model to be effective. Rego et al. developed treatment guidelines that were applicable to local conditions and using centralized expertise and frequent exchange of expertise decreased induction mortality. A similar “hub and spoke” model we developed in Georgia, South Carolina and neighboring states by using a treatment checklist and communication between APL experts and treating physicians' decreased mortality from 37% to 6.7% [Table 4](#).

5. Conclusions

We believe induction mortality in APL can be decreased and population-wide survival can be improved. Availability of standardized treatment guidelines along with support from a group of experts during induction decreases early deaths. Based on results from Brazil and our own experience, treating oncologists should be aggressively educated about early deaths and encouraged to seek advice. Our model can be implemented at the national level to improve population-wide survival in this highly curable disease.

Research agenda

- The outcomes in elderly APL patients' lags that of younger patients and trials directed towards this group will help answer these questions better.
- The use of arsenic in high risk patients and also the duration of therapy needs further clarification in prospective trials.
- Oral arsenic is presently in early clinical trials and further trials utilizing this therapy will need to careful follow up.

Conflict of interest

No relevant conflicts pertaining to this article.

Dr. Anand Jillella and Dr. Vamsi Kota received research funding from Leukemia Lymphoma Society.

Dr. Vamsi Kota served on advisory boards for Pfizer, Incyte, Novartis and Xcenda.

Appendix A. Acute promyelocytic leukemia treatment guidelines

Developed at Georgia Regents University in August 2013

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WORK-UP

BASELINE

Chest X-ray

Echocardiogram and EKG

PICC line placement – NO central lines in chest or neck or invasive procedures (bronchoscopy, spinal tap, endoscopy)

Bone marrow examination (aspirate, biopsy, flow, cytogenetics, FISH for t15:17,

PCR for PML-RAR α)

Day 14 marrow is NOT necessary.

DAILY

CBC, CMP, PT, PTT, fibrinogen TWICE DAILY until lab & clinical coagulopathy is resolved.

D-dimer ONCE DAILY for ENTIRE hospitalization.

PREVENTION/TREATMENT OF COAGULOPATHY

Intracranial, pulmonary and GI hemorrhages are frequent

Risk of hemorrhage is ↑ with the presence of any of the following - active sites of bleeding, ↓ fibrinogen, ↑ D-dimers, ↑ PT & PTT, ↑ WBC, ↑ peripheral blasts, renal failure and poor performance status;

Keep platelets above 50,000

If there are any active sites of bleeding on presentation (e.g., needle sticks, bone marrow biopsy sites,), and prolonged PT/PTT give 4 units of fresh frozen plasma (FFP) at the start of ATRA and chemotherapy.

CONTINUE FFP support TWICE A DAY until clinical bleeding resolves.

Keep fibrinogen above 150. Use 10 units of cryoprecipitate if < 150.

When clinical & lab coagulopathy is resolved, blood product support is per standard guidelines.

→ APL IS A MEDICAL EMERGENCY - START ATRA ASAP ←

PREVENTION/TREATMENT OF APL DIFFERENTIATION SYNDROME

Differentiation Syndrome symptoms are – dyspnea, unexplained fever, ↑ weight, peripheral edema, unexplained hypotension, acute renal failure, CHF, pleuro-pericardial effusions, and interstitial pulmonary infiltrates.

Daily weights - **BEDSIDE SCALES ONLY**

Keep I/O matched – **METICULOUSLY**

Diuretics if ↑ fluid retention or ↑ weight

Prednisone 0.5 to 1 mg/Kg in all patients for 2 weeks followed by a taper in the absence of leukocytosis

Increase Dexamethasone to 10 mg IV BID if onset of DS symptoms If WBC > 10,000, dexamethasone 10 mg IV bid to be started on day 1

Temporary discontinuation of ATRA or Arsenic Trioxide (ATO) is indicated in case of severe DS.

Continue dexamethasone until all symptoms are resolved. ATRA and/or arsenic can be resumed.

SUPPORTIVE CARE

Allopurinol 300 mg daily

Antibiotic prophylaxis - levofloxacin 500 mg po daily or similar antibiotic

Antifungal prophylaxis - posaconazole 200 mg po 3 × daily, voriconazole 200 mg po 2 × daily, Micafungin 50 mg daily or a similar drug.

Anti-viral prophylaxis - acyclovir 400 mg po 2 × daily or valacyclovir 1000 mg PO daily.

RBC transfusion recommended when HGB ↓ 8.

INDUCTION OF LOW AND INTERMEDIATE RISK PATIENTS

WBC < 10,000 and PLTS < 40,000 -

ATRA 45 mg/m² in divided doses twice a day plus ATO 0.15 kg daily until complete hematologic remission (no anthracycline). Prednisone 0.5 mg/kg for 14 days followed by a gradual taper if no evidence of DS.

OR

ATRA on Day 1 at 45 mg/m² DAILY in divided doses twice a day until complete hematologic remission.

Idarubicin 12 mg/m² on Days 2, 4, 6 and 8. Prednisone 0.5 mg/kg for 14 days followed by a gradual taper if no evidence of DS.

INDUCTION OF HIGH RISK PATIENTS WBC > 10,000

ATRA to be started as soon as diagnosis is suspected at 45 mg/m² in divided doses twice a day till complete hematologic remission.

Idarubicin to be started on the SAME DAY at 12 mg/M2 on days 1,

3, 5 and 7.

Dexamethasone 10 mg IV bid on days 1 to 14 followed by a taper.

Arsenic at 0.15 mg/Kg can be started on day 10

Even if the genetic results are not available, it is reasonable to start Anthracycline.

ARSENIC TRIOXIDE USE IN INDUCTION

CONSIDER ATO

Low or intermediate risk patient

Age > 60

Not a candidate for conventional chemotherapy for any reason.

Arsenic at 0.15 mg/kg daily, continued till complete hematologic remission

Combine with ATRA 45 mg/m² DAILY in divided doses

Prednisone 0.5 mg/Kg for 14 days and taper

Watch for differentiation syndrome

Watch for prolonged QTc interval

Keep Mg above 2.0 and K above 4.0

Follow LFTs for grade 2–4 liver dysfunction. If this occurs HOLD arsenic.

SUGGESTED MANAGEMENT OF ATRA/ARSENIC-INDUCED LEUKOCYTOSIS

WBC 5–50 K- Hydroxyurea 500 mg qid

WBC > 50 K- Hydroxyurea 1000 mg qid

If leukocytosis does not resolve one or two doses of Idarubicin could be considered

NO LEUKOPHERESIS.

ELDERLY PATIENTS (> 60) AND PATIENTS WITH SEVERE COMORBID CONDITIONS

May not be candidates for cytotoxic chemotherapy

Consider dose reduction of ATRA. Single agent and consider 25 mg/M2 for 14 days.

Consider dose reduction of ATO and consider 0.075 mg/M2 and add on day 15

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