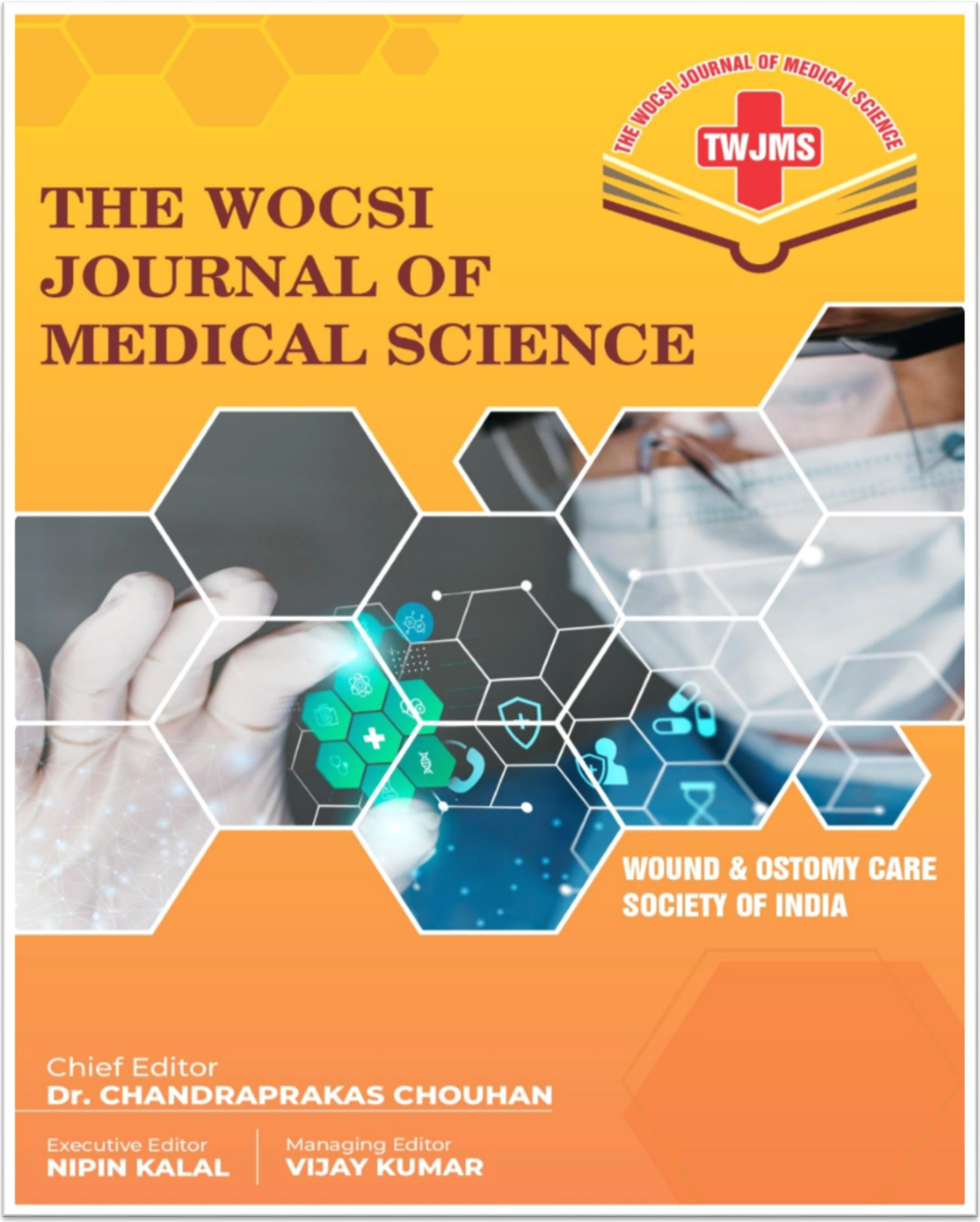
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Acute Promyelocytic Leukemia and Nursing Management: Literature Review

Parveen[1], Kumar Vijay[2], Debnath Baby Rani[3],

[1]DR. B.R. Ambedkar Institute Rotary Cancer Hospital, AIIMS, New Delhi
[2]DR. B.R. Ambedkar Institute Rotary Cancer Hospital, AIIMS, New Delhi
[3]DR. B.R. Ambedkar Institute Rotary Cancer Hospital, AIIMS, New Delhi

Abstract:

Aim of the study: This study is aimed to review the disease trajectory of APL, to describe the advances in research and clinical practice and their impact on patient outcomes.

Background: Acute promyelocytic leukemia (APL), used to be the most fatal kind of leukemia, but now with the advent of the ATRA therapy it became potentially curable subtype of adult acute myeloid leukemia. Cure of the patients with APL not only depends on the effective use of combination therapy involving differentiating and classical cytotoxic agents, but also the supportive care measures as the biology of the disease and the complications associated with molecularly targeted therapy can be fatal, if not handled proactively.

Methodology: A computerized literature search of the PubMed, Cochrane, Medline and google scholar databases in the English language was conducted using the key words "acute promyelocytic leukemia" with subheadings "anthracycline," "all-trans retinoic acid," "arsenic trioxide," "retinoic acid/differentiation syndrome," "Q-T prolongation," "disseminated intravascular coagulation" (DIC), "stem cell transplantation," and "febrile neutropenia" without specifying the year of publication. Relevant abstracts, summaries and conclusions, research articles, published guidelines etc. from national and international journals and other literary sources were reviewed.

Results: Remission induction deaths continue to represent one of the major stumbling blocks in modern therapy of APL. Many studies reported that hemorrhage is the single most common cause of death (~5%) during induction therapy, followed by infection (~2-3%) and differentiation syndrome (~1.4%) in patients with APL receiving ATRA and idarubicin (AIDA regimen).

Conclusion: Maximum deaths are happening during induction therapy; over that these are happening even before the initiation of the treatment. So, it become very critical for Oncology nurses to get acquaint themselves with the nuances of APL to play a proactive role in its management.

Keywords : Acute Promyelocytic Leukemia, Acute Myeloid Leukemia, ATRA Therapy, Oncology Nursing Management.

Correspondence : Parveen
Email : dhankaurnani2000@gmail.com

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Introduction:

Acute Promyelocytic Leukemia (APL) is a variant of AML. It used to be the most fatal kind of leukemia, but now with the advent of the ATRA (All trans-retinoic acid) therapy, it became a potentially curable subtype of adult acute myeloid leukemia.[1] It is well-established fact now that Acute Promyelocytic Leukemia being a novel entity of leukemia, must be promptly recognized and clearly distinguished from all other types of acute leukemias, particularly in light of its quick response to treatment with anthracyclines and differentiating agents such as all-trans retinoic acid (ATRA) or arsenic trioxide (ATO). [2] Cure of the patients with APL not solely depends on the effective use of combination therapy with differentiating and classical cytotoxic agents[3], however also on the supportive care measures. This is because of the biology of the disease and the complications associated with molecularly targeted therapy which could be fatal, if not handled proactively.[4] Oncology nurses ought to be aware of the complications related to APL, as they play an essential role in providing supportive care to the patients. This systematic research review provides an overview of the disease condition Acute

Promyelocytic Leukemia, including its epidemiology, pathophysiology, clinical presentation, diagnostic workup, and treatment course and complication management with perspective of an oncology nurse.

Nursing management ought to be targeted to potential complications related to disease condition and treatment-related. Complications related to Acute Promyelocytic Leukemia, include coagulopathies, differentiation syndrome, and QT prolongation with the use of arsenic trioxide, along with side effects and complications which can occur in a patient with leukemia, such as infection, hyperleukocytosis, tumor lysis, and febrile neutropenia[6]

Research question

Acute promyelocytic leukemia: role of an oncology nurse in the management of Acute Promyelocytic Leukemia patients.

Aim of the review

To overview the disease condition Acute Promyelocytic Leukemia for better evidence-based nursing management.

Objectives of the review:

- To understand the course of the disease condition
- To get accomplish with the best practices adopted to manage the disease during the course of the disease
- To broaden the nursing perspective for the better management of the disease

Inclusion criteria:

- All studies highlighting the course of the disease
- All studies clearly highlighting the nurse's role in the management of an Acute Promyelocytic Leukemia patient
- All studies available on the online platform

Exclusion criteria:

- Studies with anonymous results
- RCT's having sample size of less than 10

Methodology:

Literature search and study selection:

A literature search is made on an on-line platform like Pub Med, Cochrane, Medline, Google scholar by putting the keywords like "acute promyelocytic leukemia" with subheadings: "all-trans retinoic acid," "arsenic trioxide," "retinoic acid/differentiation syndrome," "Q-T wave prolongation," "disseminated intravascular coagulation" (DIC), "tumor lysis syndrome," and "febrile neutropenia" and "nursing responsibility", in search. Studies befitting in my inclusion and exclusion criteria were included for a systematic review. Relevant abstracts, articles, and literature were reviewed.

RESULTS:

Synthesis of data was done across the evaluations of relevant studies.

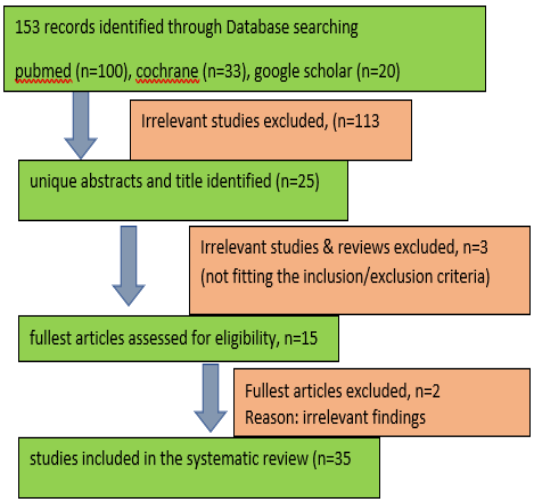

Fig 1: Schematic depiction of data collection

Approach to the patients with suspected Acute Promyelocytic Leukemia:

Although there's a general accord on the requirement to verify the diagnosis of Acute Promyelocytic Leukemia at the genetic level, but both differentiation and supportive therapy should be started before the results of genetic tests are obtained.

Rapid confirmation of the genetic diagnosis is crucial as the effectivity of differentiation treatment based on retinoids and/or arsenic derivatives is strictly based on the presence of the PML/RARA fusion in leukemia cells, genetic confirmation of this specific lesion is obligatory in all cases.

Morphologic diagnosis of hyper granular (typical) Acute Promyelocytic Leukemia is extremely prognosticative of an underlying PML/RARA rearrangement, and

Immunophenotyping by multiparameter flow cytometry can improve the accuracy of diagnosis, particularly in patients with morphologic features evoking a micro granular (variant) subtype.

Diagnostic workup and sample processing.

1. **Bone Marrow Aspirate:** may be omitted only when the peripheral blast count is high and the patient is to be thought about for palliative treatment only.
2. **Trephine Biopsy:** needed in the case of a dry marrow aspirate and wherever no abnormal cells are present in the peripheral blood (PB) to permit a morphologic and molecular identification.
3. **Immunophenotyping:** by multiparameter flow cytometry
4. **Genetic Diagnosis:**
   - Conventional karyotyping,
   - Fluorescence in situ hybridization (FISH),
   - Reverse transcriptase-polymerase chain reaction (RT-PCR) (6) or
   - Anti-PML monoclonal antibodies, respectively.

Certain favorable prognostic factors for Complete Remission are

- Younger age: Patients older than 65 years have a higher risk of early death. (Degos& Wang etal.2001) [2]

- No or mild purpura,
- High serum total protein level,
- Low lactate dehydrogenase level, and
- No or mild disseminated intravascular coagulation (DIC).

Favorable prognostic factors for EFS (event-free survival) are

- Leukocyte counts < 10.0x10(9)/l: high white blood cell count which increases the risks of leukocyte activation syndrome and relapse. [7] Mild DIC, and
- No sepsis during induction therapy.

Poor prognostic factors as reported in many studies are:

- Increased WBC count,
- Molecular features like PML/RARA isoform and FLT3-internal tandem duplication (ITD) mutations[9] and
- Immunophenotypic features like blasts of the stem/progenitor cell antigen CD34, Neural adhesion molecule (CD56), T cell antigen CD2Management of patient with Acute Promyelocytic Leukemia.

- Hospitalization of the patient throughout initial treatment is extremely advisable. The foremost critical period is the induction phase as there are quite high chances of thrombo-hemorrhagic events, cytopenia and infectious complications to happen. [10]
- It is highly needed that ATRA must be started even before the diagnosis of the disease, commencing of supportive treatment simultaneously and speedy confirmation of the genetic diagnosis. [7]

Induction treatment:

ATRA/ATO combination therapy vs. ATRA plus chemotherapy

Many studies[4,11-14] reported that ATRA/ATO combination therapy for a newly diagnosed Acute Promyelocytic Leukemia is a better treatment regimen than ATRA plus chemotherapy. Reason being,

1. There's no apparent cross-resistance between ATRA and ATO;
2. Combination of these two drugs allowed a significantly prolonged survival and
3. Combination of these two agents target PML-RARα and causes apoptosis/differentiation through distinct routes.

Arsenic trioxide thinks to have a dual mechanism to work.

1. It induces the breakdown of the promyelocytic leukemia-retinoic acid receptor alpha fusion protein.
2. It causes the induction of apoptosis, which is its second mechanism.[15-16] It can also induce CR in most APL patient's refractory to ATRA and CT. [17]

ATO in case of the second line of treatment and a single agent is capable of inducing CR in 85 to 90% of relapsed cases. Besides having a high Complete Remission rate, ATO can penetrate into the blood–brain barrier. It makes ATO a perfect salvage treatment for central nervous system diseases which have been reported in relapsed Acute Promyelocytic Leukemia cases. [17]

In case the patient's WBC more than $10X10^9$/l, hydroxyurea may be used for the initial three days and, subsequently, IA regimen (Idarubicin and Ara-C) may be initiated. [12]

Consolidation therapy:

Many studies divulged that Ara-C and anthracycline-based chemotherapy is superior to high dose anthracycline therapy in minimizing the relapse rates. High dose Ara-C is found to cause a lower additive incidence of relapse and increase the survival of high-risk patients. [19]

Three courses of recommendations are:

1. DA regimen (daunorubicin, 45 mg/m2 per day for 3 days; Ara-C, 100 mg/m2per day for 7 days),
2. Ara-C 'pulse' regimen (Ara-C, 1.5–2.5g/m2 per day for 3 days) and
3. HA regimen (homoharringtonine, 2–3 mg/m2 per day for 3 days; Ara-C, 100 mg/m2 per day for 7 days).

In the countries where homoharringtonine is unavailable, MA regimen (Mitoxantrone 6–10 mg/m2 per day for 3 days, Ara-C 100 mg/m2 per day for 7 days) may be a better substitute.

Maintenance therapy

Through various studies it is evident that the best answer to maintenance therapy is combined use of assorted medication with different therapeutic targets. On the premise of many studies, it had been devised that sequent use of ATRA, ATO, and low dose chemotherapy for 30days; 6-mercaptopurine for 30days, arsenic trioxide for 30days, or methotrexate once a week for 4 weeks is crucial for relapse-free survival and Overall Survival (OS) of the patients. CNS prophylaxis in patients is additionally advised 4–6 times using drugs like methotrexate (10–15 mg), dexamethasone (5 mg) (or Prednisolone 40 mg), and Ara-C (40–50 mg), throughout maintenance therapy. [19]

Table 1: Disease and treatment related complications

S.NO	Complications	Presnting symptoms	Management	Supportive treatment
1	**ATRA syndrome/ differentiation syndrome (DS)** most commonly related to ATRA/ATO-based treatment, however, it can occur without ATRA/ATO. [18] DS might occur within the initial week of therapy of ATRA and/or ATO and ATRA-chemotherapy and persists throughout the second and the third week. [20]	• Dyspnea, • Unexplained fever, • Weight gain, • Peripheral edema, • Unexplained hypotension, • Acute renal failure or congestive heart failure, and • Interstitial pulmonary infiltrates, or pneumopericardium effusion[2,12-13]	• Steroid therapy-dexamethasone (10 mg/12 hours till the symptoms resolve). [12,14] • ATRA therapy may be stopped for few times, till the symptoms resolve • Diuretic treatment[14] • ATRA with a tiny dose of harringtonine/mitoxantrone to scale back the incidence of intracranial bleeding because of leukocytosis	• Treatment with G-CSF not recommended. • For patients with extreme hyperleukocytosis, hydroxyurea and leukapheresis are at the physician's discretion. • Packed red cell transfusion to maintain blood hemoglobin higher than 9 g/dL.
2	**Arsenic trioxide toxicity**	• Acute renal failure, • Upper GI bleeding, • Cardiotoxicity: Salvianolic acid A (sal A) may be a major effective element in treating ATO-induced cardiotoxicity. [22] • Neurotoxicity, • Hepatotoxicity, • Sepsis etc.,	• Hospitalization: if syncope, rapid or irregular heartbeat develops • Temporarily discontinuation of ATO therapy • Once the QT/QTc returns to approximately 460-500msec, the electrolytes are repleted, Once the syncope and irregular heartbeat ceases, ATO may be resumed. • Hypokalemia or Hyperglycemia to be treated accordingly.	• ECG and electrolyte observation[12] • Monitor serum potassium concentrations • Serum magnesium concentrations • Maintain healthy Serum calcium and Serum creatinine levels
3	**Coagulopathy** It is associated with this illness and may be combined with DIC and fibrinolysis. [3] Intracerebral and pulmonary hemorrhages are comparatively common grievous complications happening when the characteristic coagulopathy of APL is active.	• Hypofibrinogenemia (100 mg/dl), • Increased levels of fibrin degradation products or D-dimers • Prolonged prothrombin time or activated partial thromboplastin time, • Leukocytosis • Abnormal levels of creatinine • Poor performance status	**In case of active coagulopathy:** •Fresh frozen plasma, cryoprecipitate, or fibrinogen to take care of a fibrinogen level more than 1.5 mg/L and hemostatic levels of coagulation factors. Tranexamic acid (100 mg/kg per day) continuous IV infusion if platelet counts less than 50 × 109/L or visible clinical-biologic signs of coagulopathy	Avoid invasive procedures like Central venous catheterization, spinal tap, and alternative invasive procedures[13] Use of recombinant factor VIIa within the state of grievous hemorrhage may be done.

4	**Hyperleucytosis** WBC >100,000/ml #often related to the M3v (microgranular variant of APL) [23]			Observation for • DIC and • Tumor lysis syndrome.
5	**Febrile Neutropenia** • absolute neutrophil count (ANC) < 1500 cells/ml • fever- oral temperature >101F (single observation) • 100.4 F for an hour	**Suspicion of sepsis:** **Look for three symptoms:** • Fever, • Mild hypotension, • Tachycardia	• Microbiological culture • Empirical antibiotic within 1hr of incidence of fever and Microbiological culture [24] • Fluid revitalization (to counter mild hypotension & tachycardia) • Blood Transfusion support • Blood glucose management as the patient is potential to sepsis	Protective precautions for neutropenic patients: [25] • Hand hygiene; • Protective gowns for expected body fluid contamination; • No guests with symptoms of respiratory infection allowed; • Private rooms with windows closed; • Negative-pressure rooms with anterooms for patients with airborne respiratory infections (e.g., meningitis or pneumonia); • High-efficiency particulate air filters; • Contact precautions • Guidelines for the handling of ice, flowers, plants, and animals.

DISCUSSION

Remission induction deaths continue to present one of the major hurdles for Acute Promyelocytic Leukemia therapy. Many studies[16,18,20,24,27-29] highlighted that hemorrhage is the single most common cause of death during induction therapy, followed by infection and differentiation syndrome in the patients receiving ATRA-based therapy. Maximum lethal hemorrhages occurred early during induction, while infection and Differentiation syndrome became the cause of deaths at later stages of the treatment regime.

A number of studies have reported optimizing the antileukemic efficacy of ATRA by using it in combination with chemotherapy for induction therapy. An increased WBC count has been reported as an independent prognostic factor of response to induction therapy in many studies. It was also observed that the presence of coagulopathy and abnormal levels of creatinine significantly posed a higher risk of mortality, most particularly, hemorrhagic mortality happened during induction remission. Hemorrhagic mortality has been observed despite generalized and early aggressive supportive care, regardless of prognostic factors. So, the acknowledgment of a particular set of prognostic factors can be useful to identify high-risk patients.

A nurse empowered with relevant and up-to-date knowledge can make a difference in the proper management of patients with APL. As studies are indicating that ATRA-based therapy is doing a wonderfully better job for APL patients, but proactive

management of the patients at initial stage of treatment is most significant. It is obvious from this review that patients with APL are highly susceptible to complications throughout the treatment process, so evidence practices are very much essential for managing such patients. An oncology nurse with expertise in early identification of the symptoms and proper management plays a significant role in the affirmative outcome of the patient. In today's era when we talk about the multidisciplinary team for positive outcome, such skills put an oncology nurse at a step ahead.

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