17 Acute Promyelocytic Leukemia in Developing Countries: A Chemotherapy-Based Approach

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Geographical Differences in APL Frequency Among AML Subtypes

Although the actual incidence of acute promyelocytic leukemia (APL) is not known, studies show that it can vary by ethnic group. Large cooperative groups in the United States and Europe have reported that APL comprises 5–13% of acute myeloid leukemia (AML) in Caucasian patients [1–4]. A population-based report from the Swedish Adult Acute Leukemia Registry that included 98% of all cases of acute leukemias found that APL constituted 3.2% of all AML cases [5]. In contrast, several studies reported an APL frequency of more than 20% among patients with AML in Latin American countries [6–11].

In 1996, Douer et al. reported a significantly higher frequency of APL (37.5% in those with AML) in patients of Latino origin than in those of non-Latino origin (6.5%) at the Los Angeles County—University of Southern California Medical Center [4]. Although this study suggested a genetic predisposition to APL, it was limited by the absence of a clear definition of the genetic background of Latinos. However, these findings were corroborated by studies reporting that APL represents 20% or more of all patients with AML in Brazil (28.2%) [6, 7], Mexico (20%) [8], Venezuela (27.8%) [9], Peru (22%) [10], and Costa Rica (34%) [11]. It is important to note that all these studies were based on hospital registries, and it was therefore not possible to estimate the actual incidence and prevalence of APL in patients from these countries. In a study data from 709 patients with APL in the Surveillance, Epidemiology, and End Results (SEER) Program, Matasar et al. [12] found that Hispanics did not have greater lifetime incidence rates than did whites. However, the age distribution for Hispanics was significantly different from that for non-Hispanic whites, with children aged 1–19 years and adults aged 20–44 years having a higher incidence of APL.

Challenges in the Diagnosis and Treatment of APL in Developing Countries

In an analysis of 157 patients with APL treated from January 2003 to March 2006 at 12 Brazilian institutions, Jácomo et al. reported a death rate of 32% during induction and 10.5% during

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consolidation and a 2-year overall survival (OS) rate of less than 60% [13]. In contrast, long-term disease-free survival (DFS) rates of approximately 85% have been reported by European and North American groups [14].

The poor outcomes of patients with APL at Brazilian institutions were attributed to a combination of factors such as high frequency of patients with severe bleeding and infectious complications at presentation, difficulties in accessing healthcare services, and delay in establishing a diagnosis and initiating specific treatment. Another important barrier in the management of patients with APL was the high cost of mandatory tests required for genetic confirmation of APL, shipping of bone marrow samples to central reference laboratories for diagnosis, and the availability of medications [13, 15].

In 2004, the International Consortium on Acute Promyelocytic Leukemia (IC-APL), an initiative of the International Members Committee of the American Society of Hematology, was created with the objective of improving the outcomes of patients with APL. The consortium published guidelines for the management of patients with APL, including diagnosis, supportive care, and specific treatment adapted to the local or regional capacities [16].

Diagnostic Tests for APL

APL is considered a medical emergency, and therefore a method for rapid diagnosis needs to be readily available. Although the morphologic and immunophenotypic features of leukemia cells are usually suggestive of the diagnosis, it is necessary to identify the APL-specific translocation t(15;17), which results in the *PML–RARA* fusion in leukemic cells, at the chromosome, DNA, RNA, or protein levels. The most common diagnostic tests are karyotyping, fluorescence in situ hybridization (FISH), and reverse transcription polymerase chain reaction (RT-PCR). Although all these methods have high specificity, some considerations need to be made when selecting an assay suited for local healthcare settings. FISH is a rapid test, but its use is limited in developing countries due to high costs. Karyotyping is expensive and time-consuming and needs specialized laboratories and personnel. RT-PCR is the gold standard to confirm the diagnosis of APL with high specificity and sensitivity and is less expensive than FISH and karyotyping; however, it takes approximately 2 days to obtain the results.

The anti-PML immunofluorescence assay is an alternative to the more sophisticated and expensive assays for confirming the diagnosis of APL. The anti-PML antibody is directed against the amino-terminal region of the human PML gene product and produces a characteristic speckled nuclear pattern that reflects the localization of the protein into discrete structures (5–20 per nucleus) called PML nuclear bodies. The architecture of PML nuclear bodies appears to be disrupted in APL cells that harbor the t(15;17), thus resulting in a change in the nuclear staining pattern from speckled (wild-type PML protein) to microgranular (PML–RARA fusion protein) (Fig. 17.1). This assay is a simple, rapid (<6 h), and inexpensive method to diagnose APL and has been essential for the success of the collaborative protocol of IC-APL [17–19].

In an interim analysis of 130 patients in the IC-APL protocol, the anti-PML assay showed excellent concordance with RT-PCR and/or karyotyping. In 15 patients, diagnosis of APL was suspected on the basis of morphologic analysis, but results of the anti-PML assay were negative. Further, RT-PCR did not reveal the *PML/RARA* rearrangement, and cytogenetic analysis did not detect t(15;17) in any of these patients. Further, of 115 patients in whom the anti-PML assay was positive, *PML/RARA* transcripts were confirmed by RT-PCR in 59, by cytogenetics in 5, and by both methods in 51 patients [19]. These findings support the agreement between the anti-PML assay and RT-PCR and cytogenetic analysis. However, although the anti-PML test is very specific, it has low sensitivity and is not reliable to monitor minimal residual disease (MRD).

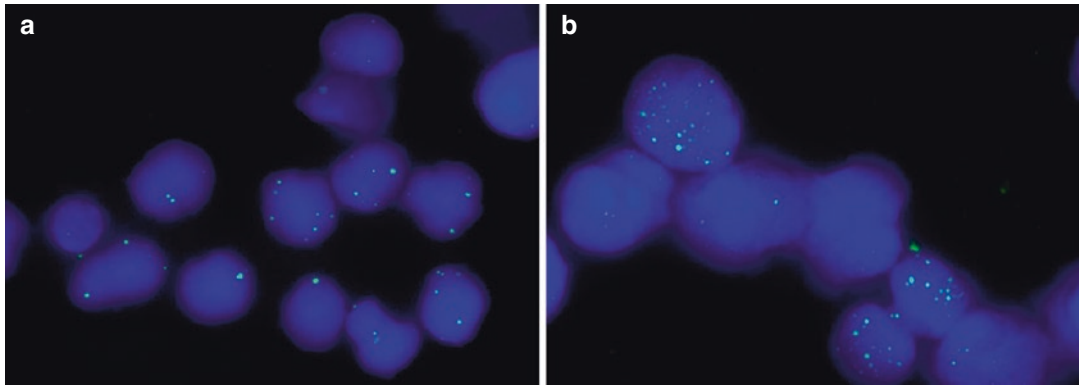

Fig. 17.1 Anti-PML immunofluorescence assay. (**a**) Negative: a characteristic nuclear speckled pattern showing the localization of the protein into discrete structures (PML nuclear bodies). (**b**) Positive: architecture of PML nuclear bodies appears to be disrupted in APL cells that harbor the t(15;17), thus resulting in a nuclear microgranular pattern (PML–RARA fusion protein)

Supportive Care Measures

The prompt initiation of all-*trans*-retinoic acid (ATRA) treatment is key to determining patient outcome, because it reduces the risk of fatal bleedings and early mortality. In the IC-APL protocol, the timely administration of ATRA was ensured by making it available in satellite pharmacies at the emergency rooms of participant institutions. ATRA treatment was initiated on the basis of suspicion of APL before genetic confirmation. In addition, aggressive transfusion support was immediately initiated to maintain platelet counts above 30,000–50,000/μL and the fibrinogen level above 150 mg/dL, and levels were monitored at least once daily [16, 19, 20].

IC-APL 2006 Treatment Regimen

The IC-APL 2006 treatment regimen consisted of the combination of ATRA and anthracycline-based chemotherapy, which was previously used in the Programa Español de Tratamiento en Hematologia/Dutch–Belgian Hemato-Oncology Cooperative Group (PETHEMA/HOVON) LPA2005 trial. However, idarubicin was replaced by daunorubicin because of its lower cost and easier availability in participating countries. Idarubicin was replaced by daunorubicin at a ratio of 1:5 (Fig. 17.2) [19].

After the genetic confirmation of APL, induction treatment was initiated with daunorubicin (60 mg/m^2/day given as an intravenous (IV) bolus on days 2, 4, 6, and 8 (except for patients aged >70 years, who received only three doses)). Oral ATRA (45 mg/m^2 divided in two daily doses or at 25 mg/m^2/day for patients aged ≤20 years) was administered until complete hematological response (CHR) was achieved. Patients with white blood cell (WBC) counts higher than 5000/μL at presentation or during the first 2 weeks of ATRA therapy received prophylaxis against differentiation syndrome (DS) with IV dexamethasone (2.5 mg/m^2/12 h for 15 days).

Patients who achieved CHR received three monthly consolidation courses with ATRA (45 mg/m^2/day divided into two daily doses for 2 weeks) and anthracycline-based chemotherapy, with the dose and duration adapted to the assessed risk of relapse, as outlined by the PETHEMA and Gruppo Italiano per le Malattie Ematologiche dell'Adulto (GIMEMA). This regimen was chosen to provide more intensive treatment for high-risk patients and minimize toxicities in low-risk patients [20, 21].

Low-risk patients received ATRA in combination with daunorubicin (25 mg/m^2 on days 1–4) in cycle 1, mitoxantrone (10 mg/m^2 on days 1–3) in cycle 2, and daunorubicin (60 mg/m^2 on day 1) in cycle 3. Intermediate-risk patients received intensified consolidation by increasing the dose

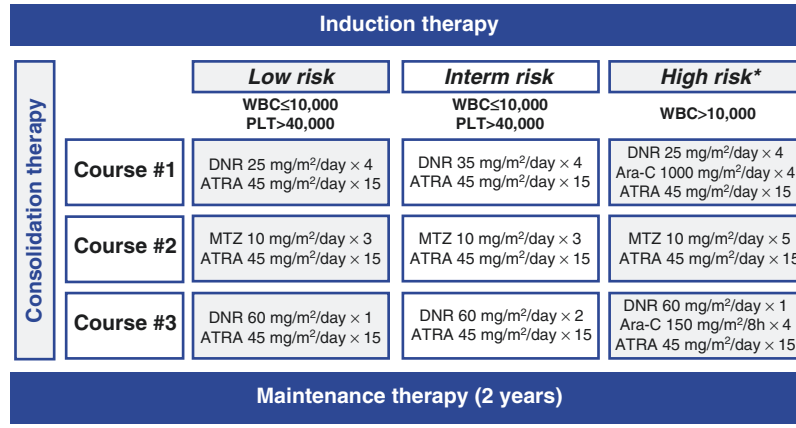

Fig. 17.2 The IC-APL 2006 treatment regimen

of daunorubicin to 35 mg/m^2 in cycle 1 and repeating the infusion at 60 mg/m^2 for 2 days in the third cycle. For high-risk patients, consolidation was further intensified by adding cytarabine in cycle 1 (1000 mg/m^2 on days 1–4) and cycle 3 (150 mg/m^2 every 8 h on days 1–4). In addition, mitoxantrone (10 mg/m^2/day) was administered for 5 days in cycle 2; the dosage of anthracyclines in cycles 1 and 3 was similar to that for low-risk patients. High-risk patients older than 60 years were treated as intermediate-risk patients.

At the end of the third consolidation, the presence of the *PML/RARA* rearrangement was assessed by RT-PCR. Patients in molecular remission received maintenance treatment for 2 years with ATRA (45 mg/m^2/day divided into two doses for 2 weeks each every 3 months) along with intramuscular or oral methotrexate (15 mg/m^2/week) and oral mercaptopurine (50 mg/m^2/day) during the ATRA pause. Central nervous system prophylaxis was not given. MRD was evaluated every 3 months for 2 years after the end of maintenance by RT-PCR for *PML/RARA*.

The IC-APL 2006 trial resulted in improved treatment outcomes for patients with APL in developing countries. The CHR rate was of 85%, and the mortality rate during induction was 15%. The main causes of early death were hemorrhage (48.1%), infection (25.9%), and DS (18.5%) [19]. Compared with the results reported by Jácomo et al. [13], there was a reduction in the mortality rate (~50%) during induction and an improvement in the 2-year OS of approximately 30% over historical controls. The DFS was 91%, and the 2-year cumulative incidence of relapse was 4.5%.

Because of the similarity in the design of the IC-APL 2006 trial and PETHEMA/HOVON LPA2005 trials [19, 21], a matched-pair analysis was performed to compare the efficacies of daunorubicin and idarubicin. Eligibility criteria for both trials were as follows: a diagnosis of de novo APL with demonstration of the t(15;17) and/or of the *PML/RARA* rearrangement in leukemic blasts, normal hepatic and renal function, no cardiac contraindication to anthracyclines, and an Eastern Cooperative Oncology Group performance status of less than 4. The study matched 175 patients in the IC-APL trial with 350 patients from the PETHEMA/HOVON LPA2005 trial [21]. Daunorubicin and idarubicin had similar antileukemic efficacy in terms of primary resistance, molecular persistence, and molecular and hematologic relapse. There were no significant differences in the number of deaths due to hemorrhage, infection, and DS between both cohorts [21].

The complete remission (CR) rate was significantly higher in the PETHEMA/HOVON (94%) cohort than in the IC-APL cohort (85%) (P = 0.002), but all induction failures in both cohorts were due to death during induction. There was also a significantly higher nonrelapse mortality rate during consolidation in the IC-APL cohort than the PETHEMA/HOVON cohort (4.8% vs. 1.2%, respectively; P = 0.04), likely due to suboptimal prevention

and treatment of infections during consolidation. Another important finding was a significantly higher DS-associated mortality among those with moderate or severe DS in the IC-APL cohort than in the PETHEMA/HOVON cohort (12% vs. 3%, respectively; $P = 0.01$), possibly due to differences in supportive care and management of DS [21]. Nonetheless, the IC-APL trial is ongoing, because it has already demonstrated that global networking and the use of protocols adapted to local resources can help reduce the gap between developed and developing countries with regard to the quality of care and treatment outcomes.

A chemotherapy-free ATRA and arsenic trioxide (ATO) regimen has recently emerged as the new standard care for patients with APL. Patients with the most curable form of AML who receive this regimen have higher cure rates than those given the standard ATRA plus chemotherapy regimen [22, 23]. Unfortunately, the high cost of ATO limits the access of this treatment for Latin American patients with APL. The results obtained for ATO by hematologists in India, where the drug is affordable, are very promising [24]. The future challenge for hematologists working in developing countries is to overcome the hurdle of ATO availability and compare the results obtained with ATRA plus chemotherapy versus ATRA plus ATO.

Lessons Learned and Recommendations

- A suspected diagnosis of APL is considered a medical emergency. ATRA and aggressive supportive care need to be initiated even before the molecular confirmation of APL.
- Anti-PML antibody test is a simple, rapid, and inexpensive method to diagnose APL.
- When used in combination with ATRA, daunorubicin and idarubicin have comparable efficacy.
- DS prophylaxis with dexamethasone (2.5 mg/m^2/12 h IV for 15 days) is indicated in patients with WBC counts higher than 5000/μL at presentation or during the first 2 weeks of ATRA.
- Risk-adapted consolidation courses provide more intensive treatment in high-risk patients and minimize toxicities in those with low-risk disease.
- Cure rates seen for patients with APL in developed countries can be achieved in developing countries by collaborative networking and using protocols adapted to local resources.

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