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REVIEW

Acute promyelocytic leukemia: What is the new standard of care?

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ABSTRACT

Acute promyelocytic leukemia (APL) is one of the most exciting stories of modern medicine. Once a disease that was highly lethal, the majority of patients are now cured with the advent of molecularly targeted therapy with all-*trans* retinoic acid (ATRA) and arsenic trioxide (ATO). In many patients, chemotherapy can be omitted completely, particularly in patients with low- or intermediate-risk disease (white blood cell count ≤ 10,000/μl). Recent data show overall survival exceeding 90% with ATRA and ATO-based induction and consolidation strategies. In the uncommon patient in whom relapse does occur, most can still be cured with ATO and autologous hematopoietic cell transplantation. Remaining challenges in APL management include the rapid identification and treatment of newly diagnosed patients to decrease the early death rate, optimizing treatment strategies in high-risk patients (white blood cell count > 10,000/μl), and the role of maintenance therapy in lower risk patients.

1. Introduction

Acute promyelocytic leukemia (APL) is a unique subtype of acute myeloid leukemia (AML) characterized by distinct morphologic and cytogenetic aberrations and a potentially life-threatening coagulopathy [1–3]. APL is defined and driven by a specific balanced translocation, t(15;17), resulting in the fusion of *PML* (promyelocytic leukemia) and *RARα* (retinoic acid receptor-α) genes. This fusion yields an aberrant, oncogenic protein (PML-RARα) that blocks myeloid differentiation at the promyelocyte stage [4,5]. Clinically, the bone marrow blast percentage in APL can be variable, and patients often present with peripheral cytopenias, including a low or normal total white blood cell count (WBC). Bone marrow promyelocytes are considered blast equivalents, can be atypical and hyper-granular, and cytolysis after chemotherapy may contribute to the coagulopathy.

APL is a rare disease (approximately 1200–1500 cases/year in the United States), accounting for approximately 10–15% of all AML cases [6]. Some cases of APL are therapy-related, occurring after exposure to cytotoxic chemotherapy (most commonly topoisomerase II inhibitors) or radiation (including radioactive iodine) for a first malignancy [7–11]. Interestingly and unlike most other AML subtypes, outcomes in de novo and therapy-related APL appear to be essentially equivalent [12]. Historically, although outcomes were favorable relative to other AML subtypes, long-term overall survival (OS) was <50% [13–16]. Many non-survivors died early in the disease course before or during induction chemotherapy from bleeding complications (most commonly cerebral hemorrhage). Relapse was common as well and required autologous or allogeneic hematopoietic cell transplantation (HCT) for sustained disease control. However, with the advent of therapies targeted to the retinoic acid receptor (RAR) over the last 1–2 decades, APL has undergone a remarkable transition from an often rapidly lethal disease with less than half of patients achieving long-term remissions to one of the most curable forms of leukemia, although early death remains a problem if treatment is delayed. In recently published reports, both event-free survival (EFS) and OS at 2–3 years have improved remarkably to approximately 90% or more [17,18].

This perspective will focus on contemporary therapy of APL with all-*trans* retinoic acid (ATRA) and arsenic trioxide (ATO), with or without chemotherapy, during all phases of treatment (induction, consolidation, and maintenance). We will also review indications for traditional cytotoxic chemotherapy using a risk-adapted approach, and discuss the treatment of relapsed disease in the era of targeted therapy. Lastly, we will address the emergent need for rapid administration of ATRA at first suspicion of APL, as this may be critical for preventing early death from catastrophic hemorrhage in what is now an imminently curable disease.

1.1. The evolution of APL therapy in the targeted era: what is the emerging treatment paradigm?

1.1.1. Induction

Before the development of ATRA, APL was treated with standard AML induction regimens including an anthracycline and cytarabine. Most patients achieved complete remission (CR) (approximately 70–

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80%), with the majority of non-CR patients dying from bleeding complications and occasionally refractory disease [13–16]. Of the patients who achieved CR, over half eventually relapsed. Two-year OS rates were approximately 30–40%.

The introduction of ATRA (which targets the RAR and induces terminal differentiation of APL blasts) into the treatment armamentarium in the late 1980s and early 1990s improved CR rates to as high as 90% (as a single agent), but early mortality remained high and APL differentiation syndrome (a syndrome manifested by fever, hypotension, fluid retention, and diffuse pulmonary infiltrates) often developed with a rapid rise in the WBC (see Table 1) [19–28]. In addition, the emergence of resistance and subsequent relapse was relatively common with ATRA monotherapy. Thus, studies were conducted showing that the ATRA plus chemotherapy was superior to ATRA alone with impressive CR rates of 90–95% [28]. Also, concurrent administration of ATRA plus chemotherapy was demonstrated to be more effective than sequential therapy and to decrease the risk of differentiation syndrome [29–31]. Standard induction regimens for newly diagnosed APL began to include ATRA and an anthracycline (+/− cytarabine) [32]. While there is no prospective randomized comparison of idarubicin versus daunorubicin in APL, retrospective data have suggested that idarubicin may be superior to daunorubicin, but either is considered acceptable [33]. Historically, the PETHEMA group has shown outstanding outcomes with idarubicin and ATRA alone (without cytarabine), while in most APL trials using daunorubicin it has typically been given in combination with cytarabine, making direct comparison of the two anthracyclines difficult.

While APL is exquisitely sensitive to anthracyclines [34], the role of cytarabine remains less clear, particularly in the ATRA era. Cytarabine has been successfully omitted from induction regimens without a negative impact on response regardless of the presenting WBC, especially if ATRA is given with both induction and consolidation and idarubicin is used as the anthracycline of choice (the idarubicin and ATRA or "AIDA" regimen) [30,31]. The Medical Research Council (MRC) has reported less myelosuppression and equivalent outcomes with AIDA compared to ATRA, daunorubicin, and cytarabine [35]. Furthermore, with the subsequent discovery of the activity of arsenic trioxide (ATO) in APL, cytarabine and in certain cases even anthracyclines may no longer be required to cure most patients.

ATO, which degrades the PML-RARα fusion protein among other anti-leukemic properties including induction of apoptosis, was shown in the 1990s to have impressive clinical activity in relapsed or refractory APL when used as a single agent, with approximately 85% of patients responding after 2 cycles (see Table 1) [36–38]. Subsequent studies demonstrated significant activity in newly diagnosed disease as well, with again approximately 85% of patients achieving CR, comparable to CR rates with ATRA plus chemotherapy [39,40]. While ATO is clearly the single most effective agent in APL, untreated patients with a relative leukocytosis (>5000/μl) may have inferior outcomes with single agent ATO compared to ATRA plus chemotherapy, with lower 3-year EFS and increased early death in one study [40]. Lastly, it should be noted that ATO can cause QT interval prolongation (>450 ms) and, potentially, cardiac dysrhythmias. Patients on ATO therapy should have regular monitoring of electrocardiograms (usually at the beginning of each cycle), additional QT prolonging agents should be avoided (such as azoles and fluoroquinolones), and potassium and magnesium levels should be maintained at normal values.

Building on pre-clinical data showing synergy of ATRA and ATO in vitro, studies combining the 2 agents with or without chemotherapy were undertaken [41,42]. A 3-arm clinical trial conducted in China comparing ATRA monotherapy, ATO monotherapy, and ATRA/ATO combination therapy showed superior outcomes with combination therapy: fewer relapses, faster achievement of CR, and greater reduction in PML-RARα transcript burden [43]. However, it should be noted that patients in this study did receive chemotherapy with consolidation and maintenance. Nonetheless, subsequent updates from this study showed durable remissions and minimal toxicity at 7 years, paving the way for ATRA/ATO combination therapy [44]. Further studies that stratified patients by risk groups showed that ATRA and ATO-based induction and consolidation therapy were highly effective in patients with low- or intermediate-risk disease (WBC ≤ 10,000/μl at initial presentation) with a CR rate of 96% and excellent long-term outcomes, despite the omission of chemotherapy from both induction and consolidation phases [45,46]. High-risk patients (WBC > 10,000/μl) had inferior outcomes on this study, despite the addition of idarubicin or gemtuzumab ozogamicin (GO) during induction. Overall, these 3 studies signified a remarkable advance in APL therapy with significant improvement in survival, although the early death rate (EDR) remained high (6–11%).

In addition, while the overall relapse rate in the ATRA/ATO era has decreased dramatically, a number of the relapses that do occur are often isolated to the central nervous system (CNS), a sanctuary site [47]. ATRA and ATO do cross the blood–brain barrier, but concentrations in the cerebrospinal fluid may not be high enough for significant anti-leukemic activity [48], possibly selecting for CNS relapse if intensive chemotherapy is not used, particularly in high-risk patients. In addition, prophylaxis with intrathecal methotrexate is also usually recommended for high-risk patients (after the achievement of CR), although there are no data to clearly establish if this strategy is protective.

In order to address some of these challenges, the Australasian Leukaemia and Lymphoma (ALLG) group conducted a trial treating 124 newly diagnosed APL patients with ATRA/ATO-based induction therapy that included a course of idarubicin for all patients [17]. Patients then received 2 courses of ATRA and ATO consolidation without chemotherapy followed by 2 years of maintenance therapy with ATRA, methotrexate, and mercaptopurine (all patients received maintenance). With minimal exposure to chemotherapy, 2-year failure-free survival was 88% and OS was 93% — only 2 patients relapsed and there were 4 early deaths. This study firmly established the role of ATRA/ATO combination therapy in APL and remains a standard current approach for the treatment of untreated APL patients, especially those with high-risk disease.

More recently, Lo-Coco and coworkers conducted a randomized phase III trial showing that ATRA and ATO induction therapy followed by 4 cycles of ATRA/ATO consolidation in low- or intermediate-risk patients (WBC ≤ 10,000/μl) is highly effective and superior to ATRA/chemotherapy-based induction, consolidation, and maintenance (no maintenance was given on the ATRA-ATO arm) [18]. Hydroxyurea was used to control the WBC in patients developing leukocytosis after exposure to ATRA (high-risk patients at diagnosis were excluded). The 2-year EFS rate was a remarkable 97% in the ATRA/ATO group compared to 86% in the ATRA/chemotherapy group ($p = 0.02$ for superiority) [Fig. 1].

In summary, ATRA and ATO are now the cornerstones of APL therapy and have dramatically improved outcomes. Based on prospective randomized trials, ATRA and ATO-based frontline therapy without chemotherapy can cure almost all patients who present with a low or normal WBC, has minimal toxicity, and can be considered the new standard of care in low- or intermediate-risk patients. However, if the WBC rises above 5000/μl after starting ATRA in a low- or intermediate-risk patient, then an anthracycline or hydroxyurea should be administered to reduce the WBC, which may ameliorate the coagulopathy and prevent APL differentiation syndrome. Lastly, patients with high-risk APL do appear to benefit from at least a short course of intensive chemotherapy during induction (+/− consolidation) and possibly also 1–2 years of maintenance therapy (see Maintenance section below).

1.1.2. Consolidation

Even with the advent of ATRA and ATO-based induction therapy, consolidation treatment is still needed to prevent relapse [49]. Risk-adapted approaches have been studied to help determine the optimal intensity and duration of post-remission therapy in both high-risk and low/intermediate-risk patients. Sanz and colleagues developed the initial prognostic system that serves as the basis for the modern risk-adapted approach: WBC >10,000/μl (high-risk), WBC ≤10,000 μl with