Modern Approaches to Treating Acute Promyelocytic Leukemia

Miguel A. Sanz and Francesco Lo-Coco

INTRODUCTION

The introduction of all-trans-retinoic acid (ATRA) in the therapy of acute promyelocytic leukemia (APL) represents the first paradigm of molecularly targeted treatment in human cancer. A number of studies conducted over the past 2 decades have contributed to the optimization of the antileukemic efficacy of this differentiating agent, especially through its combination with chemotherapy. The more recent advent of arsenic trioxide (ATO) has marked an additional milestone in APL treatment, significantly implementing the therapeutic arsenal in this disease.

After the excellent results obtained with ATO in patients who have experienced relapse, several noncomparative trials have been conducted to investigate the role of this compound in front-line treatment as an alternative to the standard combination of ATRA and anthracycline-based chemotherapy. The promising results reported in these studies have in turn inspired the design of several ATO-containing regimens to be tested in randomized studies against the conventional ATRA plus chemotherapy approach.

In this review article, we will discuss the therapeutic strategies that are currently considered state-of-the-art options in front-line treatment of APL. In parallel, we will report on several recently completed and some currently ongoing studies designed to investigate the role of ATO in different phases of the treatment of newly diagnosed patients. Finally, we will briefly discuss the available therapeutic options for relapsed APL.

TREATMENT OF NEWLY DIAGNOSED PATIENTS

Modern recommendations indicate that three simultaneous actions must be immediately undertaken when a diagnosis of APL is suspected. These include the start of ATRA therapy, the administration of supportive care with plasma and platelet transfusions, and the confirmation of genetic diagnosis. Although confirmation of APL diagnosis at the genetic level is required for patient eligibility in clinical trials, it is strongly recommended that ATRA therapy be immediately started on the basis of the sole morphologic and clinical suspect. This policy may in fact counteract, together with adequate supportive care, the severe risk of early hemorrhagic death as a result of the disease-associated coagulopathy.

Diagnostic tools to confirm APL diagnosis include polymerase chain reaction (PCR), fluorescent in situ hybridization (FISH), and/or conventional karyotyping to demonstrate the specific PML/RARA gene fusion and/or the t(15;17) translocation. A

ABSTRACT

The advent of all-trans-retinoic acid (ATRA) and its combination with anthracycline-containing chemotherapy have contributed in the past 2 decades to optimize the antileukemic efficacy in acute promyelocytic leukemia (APL), leading to complete remission rates greater than 90%, virtual absence of resistance, and cure rates of nearly 80%. Recently reported studies from large cooperative trials have also shown that more rational delivery of treatment and improved outcomes may derive from the use of risk-adapted protocols. In particular, patients at higher risk of relapse (ie, those presenting with WBC > 10 × 10^9/L) seem to benefit from treatments that include cytarabine in the ATRA-plus-chemotherapy scheme, whereas patients with standard-risk disease can be successfully managed with less-intensive regimens that contain ATRA and anthracycline-based chemotherapy. After the outstanding results with arsenic trioxide (ATO) in the treatment of APL relapse, several experimental trials have been designed to explore the role of ATO in front-line therapy with the aim not only of minimizing the use of chemotherapy but also to reinforce standard ATRA-plus-chemotherapy regimens and additionally improve therapeutic efficacy. In this review article, we discuss most recent advances in the treatment of patients with newly diagnosed and relapsed APL.

J Clin Oncol 29:495-503. © 2011 by American Society of Clinical Oncology
more recently developed assay that uses anti-promyelocytic leukemia (PML) monoclonal antibodies offers an easy, cheap, and equally specific diagnostic tool through the identification of a characteristic staining pattern of the PML protein in PML/RARA-positive APL.\textsuperscript{10-12}

### Induction Therapy

ATRA plus anthracycline-based chemotherapy as the standard approach. The simultaneous administration of ATRA and anthracycline-based chemotherapy is currently considered the standard induction treatment for newly diagnosed patients.\textsuperscript{9} This combination results in extremely high antileukemic efficacy, leading to complete remission (CR) rates of \(90\%\) to \(95\%\) (Table 1). Once the APL diagnosis is confirmed at the genetic level, primary resistance is only complete remission (CR) rates of \(90\%\) to \(95\%\) (Table 1). Once the APL diagnosis is confirmed at the genetic level, primary resistance is only

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Patients</th>
<th>Age (years)</th>
<th>Type of Chemotherapy</th>
<th>CR Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>European APL\textsuperscript{15}</td>
<td>324</td>
<td>43</td>
<td>7-77</td>
<td>90-94</td>
</tr>
<tr>
<td>French-Belgian-Swiss\textsuperscript{28}</td>
<td>312</td>
<td>47</td>
<td>NA-71</td>
<td>96.4</td>
</tr>
<tr>
<td>MRC\textsuperscript{15}</td>
<td>120</td>
<td>NA\textsuperscript{*}</td>
<td>Daunorubicin + Ara-C</td>
<td>87</td>
</tr>
<tr>
<td>GIMEMA AIDA0493\textsuperscript{70}</td>
<td>600</td>
<td>38</td>
<td>18-61</td>
<td>94.3</td>
</tr>
<tr>
<td>GIMEMA AIDA2000\textsuperscript{70}</td>
<td>420</td>
<td>41</td>
<td>18-61</td>
<td>94.4</td>
</tr>
<tr>
<td>PETHEMA LPA96\textsuperscript{14}</td>
<td>172</td>
<td>39</td>
<td>2-78</td>
<td>90.7</td>
</tr>
<tr>
<td>PETHEMA LPA99\textsuperscript{14}</td>
<td>560</td>
<td>40</td>
<td>2-83</td>
<td>91.1</td>
</tr>
<tr>
<td>PETHEMA/HOVON LPA2005\textsuperscript{19}</td>
<td>402</td>
<td>42</td>
<td>3-83</td>
<td>92.5</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete remission; APL, acute promyelocytic leukemia; Ara-C, cytarabine; MRC, Medical Research Council; NA, not available; GIMEMA, Gruppo Italiano Malattie Ematologiche dell’Adulto; AIDA, all-trans-retinoic acid plus idarubicin; PETHEMA, Programa Español de Tratamientos en Hematología; LPA, leukemia promielocitica aguda (acute promyelocytic leukemia); HOVON, Hemato-Oncologie voor Volkswassenen Nederland.

\textsuperscript{*}The study included children, adults, and elderly patients.

\textsuperscript{†}Etoposide, thioguanine, amsacrine.

followed by chemotherapy resulted in better outcomes compared with ATRA or chemotherapy alone. In both studies, in fact, the CR and early death rates were not statistically different, but the relapse rate was significantly higher for patients receiving chemotherapy alone. The outcomes with the sequential administration of ATRA followed by chemotherapy were subsequently improved in several trials in which ATRA and chemotherapy were given simultaneously. This improvement was clearly shown in a randomized study\textsuperscript{15} comparing the sequential versus the simultaneous ATRA-plus-chemotherapy schedules and was additionally confirmed in other large multicenter trials.\textsuperscript{17,23-26}

Schematically, two main chemotherapy approaches have been used in combination with ATRA. Of these strategies, one carried out by the GIMEMA and PETHEMA groups used idarubicin alone, whereas other studies included daunorubicin alone\textsuperscript{27} or in combination with cytarabine.\textsuperscript{15-17,26} Comparable CR rates have been reported with all these approaches, with no apparent advantage being observed by adding other cytotoxic agents, such as etoposide or thioguanine.\textsuperscript{17,26} To our knowledge, only two randomized trials so far have investigated the role of cytarabine for induction therapy by comparing the administration of daunorubicin\textsuperscript{25} or idarubicin\textsuperscript{26} combined or not with cytarabine. None of these trials were able to demonstrate differences in terms of either CR or induction failure rates. However, whereas the European APL study\textsuperscript{28} with daunorubicin demonstrated an increased risk of relapse when cytarabine was omitted from induction and consolidation therapy, the British Medical Research Council study (ie, MRC AML15 trial)\textsuperscript{26} found no differences in relapse and survival rates, although a small increase of deaths during remission was reported in the cytarabine arm. With respect to the direct comparison between idarubicin and daunorubicin, no prospective studies have been conducted in APL to assess the relative value of these agents when used as monochemotherapy or combined with cytarabine.

The use of alternative options to the standard approach are only recommended for patients in which chemotherapy is contraindicated (eg, those patients with severe organ failure, patients receiving anticoagulant therapy, patients older than \(80\) years, and other frail patients) or in those included in clinical trials.\textsuperscript{3} The necessity of using ATO dictated by socioeconomic factors will be discussed in the ATO As an Alternative Approach section.
Future Perspectives for Improvement

If modern induction treatment of APL results in virtual absence of disease resistance, there is no additional room for improvement except by reducing the current rate of induction death. This is an extremely challenging setting, because the relative contribution of hemorrhage, infection, and differentiation syndrome (DS) to death during induction therapy is reportedly particularly low in most recent studies.18-20,28 The identification of specific prognostic factors for each cause of induction failure may be useful for developing specific preventive measures for patients with increased probability of death from hemorrhage, infection, or DS.18

ATO As an Alternative Approach

After the excellent results with ATO in the treatment of APL relapse,1,2 several trials have explored the role of this agent in front-line therapy.3-7 Beyond its proven therapeutic efficacy, the use of ATO is regarded as an appealing option because of its apparently most favorable safety profile compared with chemotherapy, particularly with respect to myelosuppression and some uncommon late complications typically associated with the use of anthracyclines (ie, cardiomyopathy and secondary myeloid neoplasms). However, the use of ATO would not be exempt of other real or potential disadvantages. Apart from the need for daily intravenous administration for a prolonged period, treatment with ATO is associated with some electrolyte abnormalities and QT prolongation that can lead to a torsade de pointes–type ventricular arrhythmia, which can be fatal.29 Because of the high potential for embryotoxicity of this agent, ATO cannot be recommended for use at any stage of pregnancy. Finally, although long-term safety of ATO with regard to the development of secondary malignancies is uncertain, a recent report of three instances of solid tumors occurred after ATO treatment for APL30 raises the need of being alert in this respect. It should be noted that an increased incidence of malignancies has been reported in populations with environmental exposure to arsenic.31

The outcome of induction therapy with ATO is summarized in Table 2. In a variable proportion of patients in these trials, particularly those presenting with hyperleukocytosis, ATO was combined with ATRA, conventional chemotherapy or gemtuzumab ozogamicin. The CR rate in these studies was similar to that obtained with the standard ATRA-plus-chemotherapy approach, ranging from 86% to 95%. Altogether, these promising results indicate that appropriately designed comparisons of ATO-based approach with the standard ATRA-plus-chemotherapy regimens are warranted to assess efficacy, safety, and cost effectiveness of both strategies. Currently, some ongoing studies have been designed to compare standard approaches on the basis of ATRA-plus-chemotherapy or ATO-based regimens. Until the results of these trials are available, the use of ATO should be restricted to patients included in clinical trials or to those in whom chemotherapy is contraindicated. Nevertheless, it should be noted that, in countries where locally produced arsenic compounds provide a more affordable treatment than ATRA plus chemotherapy, arsenic-based regimens have been adopted as the standard of care. In this scenario, a cheaper ATO, produced under good quality control, would represent an effective and potentially curative alternative option.

Consolidation Therapy

Distinct from induction therapy, the type and intensity of consolidation, as well as the drug combination to be used in this phase, are more controversial. Nevertheless, there is a consensus on the administration of at least two to three courses of anthracycline-containing chemotherapy.9 Table 3 summarizes the standard consolidation approaches recently used in major cooperative studies. Some of these studies have highlighted the benefit of chemotherapy consolidation by showing that molecular remission (ie, PCR negativity of PML/RARA in the marrow) is now achieved in more than 99% of patients at the end of consolidation.19 The small fraction of patients with persistent molecular disease (ie, PCR positive) at the end of consolidation is currently considered the only subset in need of additional, more intensive treatments, including, when feasible, hematopoietic stem-cell transplantation (HSCT).

The Role of ATRA

Although the benefit provided by the addition of ATRA to chemotherapy for consolidation has not yet been demonstrated in randomized studies, historical comparisons of consecutive trials carried out independently by the GIMEMA20 and PETHEMA14,32 groups showed a statistically significant improvement in outcomes when ATRA was given in conjunction with chemotherapy. This suggests that ATRA contributes to reduction of the relapse risk.

Table 2. Studies Using Arsenic Trioxide for Induction Treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Daily Dose of ATO</th>
<th>No. of Patients</th>
<th>Age (years)</th>
<th>Type of Chemotherapy</th>
<th>CR Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ravandi et al7</td>
<td>0.15 mg/kg</td>
<td>82</td>
<td>47</td>
<td>14-81</td>
<td>91.5</td>
</tr>
<tr>
<td>Ghavamzadeh et al4</td>
<td>0.15 mg/kg</td>
<td>111</td>
<td>27</td>
<td>6-79</td>
<td>85.6</td>
</tr>
<tr>
<td>Mathews et al5</td>
<td>10 mg*</td>
<td>72</td>
<td>28</td>
<td>3-75</td>
<td>86.1</td>
</tr>
<tr>
<td>Shen et al3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm 1</td>
<td>0.16 mg/kg</td>
<td>20</td>
<td>39.5</td>
<td>15-69</td>
<td>90.0</td>
</tr>
<tr>
<td>Arm 2</td>
<td>0.16 mg/kg</td>
<td>21</td>
<td>34</td>
<td>14-62</td>
<td>95.2</td>
</tr>
<tr>
<td>Hu et al8</td>
<td>0.16 mg/kg</td>
<td>85</td>
<td>NA</td>
<td>ATRA 25 mg/m²</td>
<td>94.1</td>
</tr>
</tbody>
</table>

Abbreviations: ATO, arsenic trioxide; CR, complete remission; ATRA, all-trans-retinoic acid; GO, gemtuzumab ozogamicin; NA, not available; CHT, chemotherapy. 0.15 mg/kg in children.†One or two doses of an anthracycline if refractory differentiation syndrome or WBC > 50 109/L.
The Role of Cytarabine

From the first successful regimen that used daunorubicin as monotherapy, to the present, the role of cytarabine in APL has remained controversial. None of the studies conducted in the pre-ATRA era, including a randomized one, showed an advantage from adding cytarabine to anthracyclines compared with high-dose anthracyclines used as single agents. Several studies carried out during the ATRA era have contributed to the investigation of the role of cytarabine. In this regard, the study conducted in younger patients by the European APL group, in which two similar approaches with daunorubicin alone and daunorubicin plus cytarabine were randomly compared, showed a better outcome for patients in the cytarabine-containing arm. However, a subsequent joint analysis of the PETHEMA and the European APL groups confined this benefit to patients with WBC counts greater than $10 \times 10^9$/L, which showed a trend toward better outcome in this group only. In this study, the PETHEMA approach with ATRA plus idarubicin/mitoxantrone alone yielded even fewer relapses than ATRA plus daunorubicin and cytarabine in patients with WBC lower than $10 \times 10^9$/L, despite being less myelosuppressive; fewer relapses therefore led to significantly shorter hospital stays and less mortality in CR. Another study by the Medical Research Council in the United Kingdom has contributed to define the role of cytarabine in treating APL. The preliminary results of the MRC15 trial, which have been published only in abstract form to date, showed no benefit for patients in the cytarabine arm compared with those in the ATRA-plus-idarubicin arm on the basis of the Spanish PETHEMA approach, irrespective of risk category.

With regard to the role of cytarabine in consolidation therapy, two recent studies carried out separately by the GIMEMA and PETHEMA groups have demonstrated an improved antileukemic efficacy of the cytarabine-enriched schedule in high-risk patients younger than 60 years. However, the different way in which both studies have substantiated this improvement merits additional discussion. In fact, the GIMEMA study showed a dramatic reduction of the relapse rate when, in the LPA99 protocol, cytarabine was added to the consolidation therapy administered in the LPA99, which was based on the combination of ATRA and anthracycline/anthraquinone monochemotherapy. Taken together, these results indicate a possible supra-additive effect of the combination of ATRA plus cytarabine that might underlie the improvement observed in high-risk patients, as also suggested by in vitro studies.

In summary, the majority of studies suggest a potential benefit in terms of reduction of relapse risk for the addition of cytarabine in patients younger than 60 years with WBC higher than $10 \times 10^9$/L.
Furthermore, it seems that the combination of this drug with ATRA may have a supra-additive effect.

**The Role of ATO**

The role of ATO in postinduction therapy for patients with newly diagnosed APL has been explored not only with the aim to minimize or even eliminate chemotherapy but also to reinforce standard ATRA-plus-chemotherapy regimens. This latter strategy has been explored in two studies recently conducted in the United States.\(^37,38\) A large, randomized study by the US Intergroup\(^37\) showed significant improvements in event-free and overall survival outcomes for patients receiving two courses of ATO (ie, 5 days a week for 5 weeks in each cycle) given immediately after CR and before the standard postremission regimen (ie, ATRA plus chemotherapy) compared with those receiving only ATRA-plus-chemotherapy consolidation. This interesting study, however, does not definitively clarify whether reinforcement of consolidation therapy with ATO improves the outcome of standard therapy, because overall survival in the control arm was relatively low compared with rates reported by other groups that used ATRA and anthracycline chemotherapy–based schedules.\(^19,20,28\) Future studies are warranted to investigate whether the inclusion of ATO can allow de-intensification of APL therapy without compromising cure rates or even improve outcomes currently achieved with optimal ATRA and anthracycline-based protocols.

**Risk-Adapted Postremission Therapy**

In general, there is a tendency to design risk-adapted strategies to modulate treatment intensity in consolidation according not only to age, assuming that older patients are more vulnerable to chemotherapy toxicity with higher rates of neutropenic sepsis and increased treatment-related mortality, but also to predefined risk factors for relapse,\(^39\) particularly presenting high WBC counts. It should be noted that, even with therapeutic approaches that have demonstrated a relatively low toxicity, mortality rate in CR ranged from less than 1% in patients younger than 60 years to 19% in patients older than 70 years.\(^40\) Therefore, it is reasonable to design therapeutic strategies aiming to reduce morbidity and mortality as a result of chemotherapy in elderly patients and particularly in those unfit to receive more intensive therapy. As discussed previously, ATO might be a reasonable alternative option in these instances.

Tailored strategies seem to be an efficient approach to minimize toxicity and target more intensive therapy to those patients who have increased risk of relapse. In this regard, several major cooperative groups have traditionally designed consolidation therapy adjusting chemotherapy intensity to age, as previously mentioned, with a variable cutoff point at 60 or 70 years, and WBC counts, with the most common cutoff point being \(10 \times 10^9/L\).\(^19,20,28\) In addition to this strategy, the most recent PETHEMA trials (LPA99 and LPA2005) have also adjusted consolidation therapy to two additional relapse risk settings identified among those patients with WBC lower than \(10 \times 10^9/L\). These categories were defined as low- and intermediate-relapse risk groups on the basis of platelet counts greater or lower than \(40 \times 10^9/L\), respectively.\(^39\)

Other strategies have been recently proposed to allow more tailored postremission therapies by means of a rigorous and reliable sequential real-time quantitative polymerase chain reaction (RT-PCR) monitoring of PML-RARA.\(^41\) Previous studies suggested that minimal residual disease monitoring by reverse transcriptase PCR (RT-PCR) could be used to predict relapse and to direct pre-emptive therapy.\(^42,43\) By using an implemented assay that is based on RT-PCR, the Medical Research Council group has recently reported encouraging results directing pre-emptive therapy with ATO and guiding the use of transplantation in those patients who experienced molecular disease persistence or molecular relapse after front-line therapy with standard ATRA and anthracycline-based chemotherapy. This group has shown that sequential RT-PCR monitoring may overcome some of the limitations of the conventional qualitative RT-PCR assays for clinical decision making, particularly the false-negative results as the lack of capacity to distinguish between decreasing and increasing levels of leukemia-specific transcripts.\(^44\) However, it remains to be established whether the RT-PCR approach can at present be considered a standardized, cost-effective, and universally available method for routine laboratories and, therefore, be used to direct a more individualized therapy out of the context of clinical trials.
LPA 0406 trial on comparing two completely different strategies in patients with WBC less than 10 × 10^9/L, one being the classical AIDA (without cytarabine) and the other a chemotherapy-free scheme consisting of an ATO-plus-ATRA combination, as reported by the M. D. Anderson group. 69 A similar randomized study has been initiated by the British National Cancer Research Institute (NCRI AML17 trial), which includes all patients, regardless of the WBC count. In the context of ATRA plus anthracycline-based chemotherapy, the still-ongoing APL204 study of the Japan Adult Leukemia Study Group (JALSG) is a randomized, phase III trial to compare the standard ATRA versus the new synthetic retinoid, tamibarotene (Am80), as maintenance therapy. Finally, the PETHEMA and HOVON groups have planned a study to test the benefit provided by adding two courses of ATO given immediately after CR and before the ATRA-plus-chemotherapy consolidation. Risk-adapted chemotherapy will be the same as in the PETHEMA/HOVON LPA2005 trial except for the omission of the second cycle of mitoxantrone. The results derived from these investigations will likely provide relevant insight into the most appropriate combination of chemotherapy and differentiating agents by adapting their use and intensity to the risk of relapse.

**Maintenance Therapy**

The benefit provided by ATRA-based maintenance therapy in two randomized studies 33, 34 has been questioned in a large study of the Italian GIMEMA group, which has been published to date only in abstract form. 69 This study was unable to demonstrate a significant benefit of maintenance therapy when using ATRA with or without mercaptopurine and methotrexate in patients treated with the AIDA 0493 protocol. Two additional randomized trials exploring the role of ATRA-based maintenance are still ongoing (Table 4). A study from the North American Intergroup (C9710 study) compares 1-year maintenance with ATRA alone versus ATRA plus mercaptopurine and methotrexate, 77 whereas a trial of the JALSG is comparing ATRA versus the synthetic retinoid tamibarotene (Am80). It should be noted that none of these studies have included an arm without maintenance therapy except, as far as we know, a previous Japanese study that compared no maintenance versus six courses of intensified maintenance chemotherapy without ATRA. 50 This latter study showed no benefit from using chemotherapy alone in terms of reducing relapse rate; moreover, it was associated with a significantly poorer chance of survival for patients in the maintenance arm.

**TREATMENT OF PATIENTS WHO EXPERIENCED RELAPSE**

Because the standard front-line approach discussed in the Induction Therapy section is able to cure the vast majority of patients (up to 80%), data on APL relapse in the ATRA era are limited to few studies, including small series. 1, 2 For the same reason, only nonrandomized studies have been conducted so far to compare distinct strategies for relapsed APL, such as, for example, ATO-based regimen versus ATRA plus chemotherapy as salvage therapy. Finally, some patient- and disease-related variables contribute to limiting the feasibility of randomized studies in the context of relapsed APL. These variables include patient age and performance status, previous therapy, duration of first CR (CR1), molecular status after initial therapy of relapse, and donor availability.
Because of these considerations, the available data on treatment of APL relapse basically rely on a number of phase II, nonrandomized trials that use ATO in various combinations and include in some cases historical comparisons with previously adopted ATRA plus chemotherapy regimens.1,2 Similarly, only two historical comparisons have been reported to date that investigate the advantage of pre-emptive therapeutic intervention at the time of molecular relapse with respect to treating full-blown (hematologic) disease recurrence.42,43 In this respect, we believe that design of a randomized study comparing pre-emptive versus delayed treatment would be ethically questionable because of the obvious advantage provided by pre-emptive treatment on counteracting early hemorrhagic mortality. Here, we will discuss briefly the available treatment approaches for patients experiencing relapse after ATRA-based regimens. Hence, studies related to the use of HSCT in the pre-ATRA era will not be considered.

Remission Reinduction

ATO-based approach. After the initial reports from China,31 several groups confirmed the high efficacy of ATO for patients with APL who experienced relapsed after ATRA-based regimens. In particular, a US multicenter trial showed that two courses of ATO were able to induce molecular remission in nearly 80% of patients with APL treated at relapse.52,53 On the basis of these data, ATO was approved in the United States and Europe for the treatment of relapsed and refractory APL. Additional studies have successively reproduced these excellent results,54-58 reporting rates of second CR of 80% to 90% and overall survival at 1 to 3 years of 50% to 70%. ATO is administered intravenously at a recommended dose of 0.15 mg/kg/d until hematologic remission or for a maximum of 60 days. ATO is in general well tolerated, with only mild toxic effects reported in the majority of patients; however, in a sizable fraction of patients, more severe complications may occur. These consist of the occurrence of differentiation syndrome and prolongation of the QT interval. Both complications may however be successfully counteracted if promptly recognized and treated according to specific recommendation.9 Of interest, the degree of hematologic toxicity with ATO is modest; combined with the proven efficacy to reinduce molecular CR, this has contributed to consider ATO as the most convenient bridge to transplantation.

ATRA-Plus-Chemotherapy Approaches

Before the advent of ATO and the demonstration of its striking activity in relapsed APL, salvage therapy consisted of a reinduction with ATRA and chemotherapy, usually followed by consolidation with additional chemotherapy and HSCT. Chemotherapy for reinduction generally included an anthracycline or mitoxantrone and intermediate or high doses of cytarabine, with or without etoposide. These regimens resulted in high rates of second CR (80% to 90%).43,59-61 As discussed for front-line therapy, early evaluation of response to reinduction therapy by molecular or cytogenetic tests is not recommended and might provide misleading results.

Consolidation and Role of HSCT

Consolidation therapy before the ATO era usually consisted of ATRA plus chemotherapy with the same agents used to reinduce CR, followed when feasible by HSCT. Since the availability of ATO, for patients who underwent rescue with this agent, an international panel of experts on behalf of the European LeukemiaNet recommends the use of an additional course of ATO and ATRA as consolidation.9 This approach should be followed by molecular assessment of response by PCR of PML/RARA. The results of molecular response to therapy after two cycles of ATO (one induction and one consolidation course) should then be taken into account for additional decisions on the continuation of therapy and, in particular, to identify patients at higher risk of additional relapse (ie, those with persistent PCR positivity) who must be, when feasible, allocated to allogeneic HSCT.

As to successive consolidation, there is some evidence to suggest that treatment intensification with HSCT62 or chemotherapy63 may improve outcomes of patients achieving second remission with ATO. Therefore, the available options include continued treatment with ATO and/or chemotherapy plus ATRA followed by HSCT. In addition to patients who are unable to achieve a second molecular CR, allogeneic HSCT could be also recommended for those with short CR1 duration, regardless of the molecular status after salvage therapy.9 For patients with prolonged CR1 (> 1 year) who are in second molecular CR, the choice on successive therapy will vary depending on several parameters; distinct strategies are available and include HSCT, additional cycles of ATO, and/or intensive chemotherapy with or without ATRA. With regard to the choice of autologous or allogeneic HSCT in patients in whom both options are feasible, both procedures are valid therapeutic and potentially curative options. This was shown in a large survey of the European Cooperative Group for Blood and Marrow Transplantation conducted in 625 patients with APL who had received HSCT after 199364 (ie, in patients presumably treated front-line with ATRA). This study reported similar outcomes with autologous or allogeneic HSCT, and the higher risk of relapse in the autologous group was balanced by increased nonrelapse mortality in the allogeneic HSCT setting.

Management of CNS Relapse

Recently, two large studies have demonstrated a relatively low incidence of CNS involvement at first relapse in patients with APL who are receiving front-line therapy with ATRA and anthracycline-based chemotherapy without specific CNS prophylaxis.65,66 The cumulative incidence of relapse in the CNS was reported to be 1.1% at 3 years in the joint study of the PETHEMA and the European APL groups and was reported to be 1.2% at 5 years in a distinct cohort of patients in a recent study of the PETHEMA group. However, both studies reported a significantly higher incidence of CNS involvement in patients with initial WBC greater than 10 × 109/L (5% and 5.5%, respectively). In addition to hyperleukocytosis, the PETHEMA study also identified the previous occurrence of CNS hemorrhage during induction as an independent risk factor for CNS relapse. Although the precise impact of using CNS prophylaxis in APL remains unclear at present, the available data suggest that it could reasonably be restricted to patients with hyperleukocytosis at presentation and to those experiencing intracranial hemorrhage before or during induction.

FUTURE PERSPECTIVES

APL represents both a paradigm for successful targeted treatment and a model for investigation in translational medicine and oncology. The past 2 decades have witnessed remarkable advances at the laboratory and clinical level that have transformed this once rapidly fatal disease
into the most curable acute leukemia. These advances include the advent of ATRA, the discovery of the APL-specific genetic aberration to improve diagnosis and better assess treatment response, the refinement of combinatorial ATRA plus chemotherapy regimens, the use of molecularly driven protocols, the adoption of risk-adapted strategies, and the introduction of ATO in the therapeutic arsenal. The integration of these strategies is still being investigated and refined in currently ongoing clinical trials and in translational research projects. The most challenging issues include the reduction of the early hemorrhagic death rate and the possibility of minimizing chemotherapy through the use of ATO and ATRA in front-line treatment. Finally, it is hoped that lessons learned from this leukemia entity will be relevant to better design targeted therapies and assess response to treatment in other AML subsets.

REFERENCES

1. Douer D, Tallman MS: Arsenic trioxide: New clinical experience with an old medication in hemato-
    Cancer 5:183-191, 2006
3. Shen ZK, Shi ZZ, Fang J, et al: All-trans retinoic acidAs2O3 combination yields a high quality
    remission and survival in newly diagnosed acute promyelocytic leukemia. Proc Natl Acad Sci USA
    101:5329-5335, 2004
    ia without ATRA and/or chemotherapy. Ann Oncol 17:131-134, 2006
    diagnosed acute promyelocytic leukemia: Durable remissions with minimal toxicity. Blood 107:
    2627-2632, 2006
7. Ravandi F, Estey E, Jones D, et al: Effective treatment of acute promyelocytic leukemia with all-
    trans-retinoic acid, arsenic trioxide, and gemtu-
    based therapy in newly diagnosed acute promyelocytic leukemia. Proc Natl Acad Sci U S A
    106:3342-3347, 2009
    ommendations from an expert panel on behalf of the European LeukemiaNet. Blood 113:1875-1891,
    2005
    chemical diagnosis of acute promyelocytic leu-
    kemia (M3) with the monoclonal antibody PG-M3
7
    lyzing the immunocytochemical pattern of the PML
7

    protein with the monoclonal antibody PGM3. Am J
    Clin Pathol 114:786-792, 2000
    antibody (PG-M3) for rapid and accurate genetic
diagnosis of acute promyelocytic leukemia. Ann
    hematol 83:687-690, 2004
    sion induction with or without all-trans retinoic acid
    in acute promyelocytic leukemia. Br J Haematol
    103:889-898, 2000
    adapted treatment of acute promyelocytic leukemia
    with all-trans retinoic acid and anthracycline mono-
    chemotherapy: A multicenter study by the PETHEGA
    followed by chemotherapy and ATRA plus chemotherapy and the role of maintenance therapy in
    newly diagnosed acute promyelocytic leukemia: The European APL Group. Blood 94:1192-1200,
    1999
    molecular remission predict prognosis in acute
    promyelocytic leukemia treated with all-trans retinoic acid. Result of the randomized MRC trial. Blood
    93:4131-4143, 1999
17. Lengfelder E, Reichert A, Schoch C, et al: Double induction strategy including high dose cytara-
    bin in combination with all trans retinoic acid: Effects in patients with newly diagnosed acute
    promyelocytic leukemia. Leukemia 14:1362-1370,
    2000
18. de la Serna J, Montesinos P, Vellenga E, et al:
    Causes and prognostic factors of remission induc-
    tion failure in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and
    leukemia based on all-trans retinoic acid and anthracy-
    cline with addition of cytarabine in consolidation
    therapy for high-risk patients: Further improvements
    in treatment outcome. Blood 115: 5137-5146, 2010
    line treatment of acute promyelocytic leukemia with
    AIDA induction followed by risk-adapted consolida-
    tion for adults younger than 61 years: Results of the
    AIDA-2000 trial of the GIMEMA group. Blood 116:
    3171-3179, 2005
    acute promyelocytic leukemia: Results of a multi-
    center randomized trial. Blood 82:3241-3249, 1993
    All-trans retinoic acid in acute promyelocytic leuke-
    cular remission in PML/RARA-positive acute promyelocytic leukemia by combined all-trans reti-
    noic acid and idarubicin (AIDA) therapy: Gruppo Italiano-Malattie Ematologiche Malgine dell’Adul-
    to e Associazione Italiana di Ematologia ed Oncologia Pedi-
    prognostic factors in newly diagnosed acute promy-
    elocytic leukemia treated with all-trans retinoic acid
    and chemotherapy: Japan Adult Leukemia Study Group.
    consolidation results in high antileukemic efficacy
    and reduced toxicity in newly diagnosed PML/
    RARA-positive acute promyelocytic leukemia: PETHEMA
26. Burnett AK, Hills RK, Grimwade D, et al: Idarubicin and ATRA is as effective as MRC chem-
    otherapy in patients with acute promyelocytic leu-
    kemia with lower toxicity and resource usage:
    Preliminary results of the MRC AML15 trial. Blood
    110:589, 2007 (abstr 589)
    Improving the treatment outcome of acute promy-
    elocytic leukemia in developing countries through
    Leukemia Study Group. Blood 114:8, 2009 (abstr 6)
    ine useful in the treatment of acute promyelocytic
    leukemia? Results of a randomized trial from the
    European Acute Promyelocytic Leukemia Group.
29. Barby JT, Pezzullo JC, Soignet SL: Effect of
    arsenic trioxide on QT interval in patients with
    advanced malignancies. J Clin Oncol 21:3609-3615,
    2003
    acute promyelocytic leukemia Leukemia Res 31:
    105-108, 2007
    Murshidabad: One of the nine groundwater arsenic
    affected districts of West Bengal, India—Part 1. Magnitude of contamination and population at risk.
    Clin Toxicol 43:822-834, 2005
32. Sanz MA, Montesinos P, Vellenga E, et al: Risk-adapted treatment of acute promyelocytic leu-
    kemia with all-trans retinoic acid and anthracycline

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Miguel A. Sanz, Francesco Lo-Coco Collection and assembly of data: Miguel A. Sanz, Francesco Lo-Coco Data analysis and interpretation: Miguel A. Sanz, Francesco Lo-Coco Manuscript writing: Miguel A. Sanz, Francesco Lo-Coco Final approval of manuscript: Miguel A. Sanz, Francesco Lo-Coco

© 2011 by American Society of Clinical Oncology

Information downloaded from jco.ascopubs.org and provided by at Christian Medical College-Vellore on August 9, 2011 from Copyright © 2011 American Society of Clinical Oncology. All rights reserved.