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Treatment of Acute Promyelocytic Leukemia for Older Patients

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Abstract

Acute promyelocytic leukemia (APL) represents a remarkable disease in which leukemogenesis is driven by the *PML-RARα* oncogene and for which targeted treatment with all-trans retinoic acid (ATRA)–based therapy allows substantial chance of cure. APL is seen in a small subset of older patients, with age representing one of the most important prognostic factors for outcome of treatment. Unlike other acute leukemias, the inferior outcomes for APL in older patients relates less to changes in disease biology and more to increased toxicity of ATRA and chemotherapy combination regimens used to induce hematologic and molecular responses. Risk-adapted strategies that use less-toxic agents, such as arsenic trioxide, allow treatment of older patients, with greater efficiency and better chances of cure.

Keywords

Older patient; all-trans retinoic acid; acute promyelocytic leukemia; arsenic

The treatment of AML in older patients remains challenging.¹ Both disease- and patient-related factors unfavorably influence patient outcome, with a 2-year probability of overall survival of 10% to 15%.² Acute promyelocytic leukemia (APL) remains a notable exception. APL represents a model of chromosomal translocation–driven leukemogenesis. The t(15;17)–derived fusion transcript *PML-RARα* leads to transcriptional repression of differentiation-associated genes, with maturation blockade at the promyelocytic stage. Cytopenias and coagulation disorders³ lead to the diagnosis of the disease. APL represents one of the areas showing the most success with targeted therapy using all-trans retinoic acid (ATRA) and, more recently, arsenic trioxide (ATO), both of which specifically target *PML-RARα*.^{4,5}

Although current treatment strategies lead to cures in 70% to 80% of patients with APL, outcomes in older patients remain inferior,^{6,7} and age remains a prominent prognostic factor.⁸ This article describes the different treatment approaches and proposes a treatment algorithm for this specific population.

Epidemiology of APL in Elderly Patients

According to prospective clinical trials, APL constitutes 5% to 8% of AML in older patients, with 15% to 25% of the total cases occurring in patients older than 60 years. The frequency

of APL in older patients may be underestimated because many are not enrolled in clinical trials.^{9–11}

Therapy-related APL^{12,13} was recently noted after the use of topoisomerase II inhibitors for the treatment of cancer (or multiple sclerosis in the case of mitoxantrone). The average age of patients affected is usually older than those with de novo APL, with a significant proportion being 60 years or older. Disease characteristics are similar to those of de novo APL, with a possible increase in the frequency of additional chromosomal abnormalities but apparently no specific impact on prognosis. These patients usually are excluded from clinical trials of de novo APL.

Although the impact of comorbidities^{14,15} on the outcome of conventional chemotherapy^{16,17} has been studied, data are not available for APL. ECOG performance status, creatinine, and serum albumin have been reported as potential prognostic factors influencing early mortality.¹⁰ Recent data from the Programa para el Estudio de la Terapéutica en Hemopatía Maligna (PETHEMA) suggest 60 years as a cutoff age above which toxicity seems to be increased.¹⁰ Therefore, “older patients” in this article refers to those older than this cutoff age.

Diagnosis of APL: Specific Characteristics in Older Patients

The diagnosis of APL is a medical emergency and should be treated accordingly. In the older population, many common causes of bleeding may be considered before APL is suspected, which may delay initiation of therapy. The authors strongly recommend that any patient suspected of having APL (i.e., AML clinical presentation with disseminated intravascular coagulation [DIC]) be treated for the disease with ATRA until the diagnosis is excluded. Diagnosis of APL has been hastened by the introduction of standardized polymerase chain reaction (PCR) methods and, more recently, the availability of immunostaining-based assays.¹⁸ Different studies have reported conflicting results regarding disease characteristics in older patients at diagnosis. The presenting WBC count, frequency of coagulation disorders, and risk categories according to the Sanz classification seem to be mostly similar between older and younger patients with APL,¹⁹ although some studies report a slight increase of higher-risk patients among the older population.²⁰ The microgranular variant of APL may be more common in older patients. Patients with these leukemias not only have similar cytogenetic²¹ and fusion gene abnormalities but also frequently have a *FLT3-TKD* mutation.^{22,23} All patients with APL must be included in clinical trials and registries so that important clinical information can be obtained for all age groups.

Induction Therapy

Induction is the most critical period during the treatment of an older patient with APL. This article discusses supportive care and induction regimens separately. Figure 1 proposes a treatment strategy integrating the literature data described later.

Supportive Care

Early death is the principal cause of failure in older patients with APL,⁴ and age represents the main independent factor predicting early death in prospective trial analysis. Moreover, early death rate is presumably underestimated in prospective trials. Population-based studies showed that early death rate could reach up to 20%, even in locations with dense medical networks.²⁴ More than 60% of induction deaths occur during the first 2 weeks of treatment.¹⁰ High WBC count (with a cutoff value of 10,000 mcL) is also a predictor of early death in most studies. Early diagnosis, introduction of ATRA if APL is suspected, and

aggressive supportive care for the treatment of DIC are key factors in limiting early death. Leukapheresis for patients with high a WBC count should be avoided in APL in general, but particularly in older patients because of cardiovascular and coagulation risks.²⁵ APL differentiation syndrome may be a frequent cause of death in older patients.²⁶ Complications of myelosuppression are also frequent causes of death.²⁷

Use of corticosteroids to prevent differentiation syndrome should be carefully considered in older patients. These patients are at greater risk of death from this complication but are also at risk of complications from steroids.²⁵ The authors generally recommend corticosteroid use in patients with a WBC count greater than 10,000 mcL, but the decision must be individualized. Holding ATRA may be an alternative in patients with differentiation syndrome; however, shorter exposure to ATRA seems to impair prognosis.²⁸

Induction Regimen

Most collaborative groups tend to treat older patients with ATRA and chemotherapy combination regimens similar to those used in younger patients. This strategy leads to clear success with an impressive response rate, but at the price of a dramatic increase in early death rates. Some clinical trials are decreasing the intensity of induction therapy to limit toxicity.^{29,30} These less-toxic regimens will also allow these treatment strategies to be used in some patients who are considered “unfit” for chemotherapy.

As shown in PETHEMA²⁰ and GIMEMA,²⁶ conventional treatment uses a combination of ATRA and anthracycline-based chemotherapy, which may include cytarabine^{19,31} (Table 1). Complete remission rates range from 73% to 86%, and the complete molecular response rates after consolidation range from 68% to 92%.

More recently, ATO⁷ was introduced in patients with untreated APL. This agent, which induces molecular remissions in most patients experiencing relapse, shows a similar toxicity profile in younger and older patients.³⁰ ATO has been used as a single agent^{32–34} and in combination therapy with ATRA.^{35–37} Results of these trials are summarized in Table 1; however, not all studies presented specific data for older patients. Complete remission rates for ATO-based induction range from 86% to 94%. Molecular responses after induction range from 76% to 100%. In patients with a high WBC count at diagnosis or after the beginning of treatment, cytoreduction is mandatory to limit the risk of differentiation syndrome and may be performed with various agents, including hydroxyurea,³⁸ anthracyclines, cytarabine, or gemtuzumab ozogamicin.^{30,36} ATO is associated with QT prolongation and electrolyte loss (mainly potassium and magnesium), which may represent an important issue in older patients. During treatment, the authors recommend close monitoring of EKG and serum biochemistry (once or twice a week), with early electrolyte replacement if needed.

Consolidation Therapy

Three key points must be considered regarding consolidation therapy in older patients with APL: 1) the risk of relapse is similar to younger patients when treated with conventional treatments (ATRA plus chemotherapy); 2) the ongoing goal of consolidation in older patients is to obtain a molecular remission; and 3) the risk of toxic death is increased in older patients treated with conventional regimens who are in complete remission,^{26,27} and is mainly related to myelosuppression.

As with induction therapy, many studies have the goal of decreasing the intensity of consolidation therapy. Some studies focused on the elimination of cytarabine, showing no difference between cytarabine-containing and cytarabine-free chemotherapy.³⁹ High-risk

patients may have a lower relapse rate when cytarabine is added^{28,40}; however, this more-toxic strategy may be limited in patients older than 60 years. Most regimens use 2 to 3 cycles of ATRA plus anthracycline.

Two studies also evaluated the use of ATO in consolidation after conventional induction. A small phase II study³⁸ showed that one cycle of combined chemotherapy (daunorubicin plus cytarabine) and ATO led to a disease-free survival rate of 90%. The North American Leukemia Intergroup C9710 study⁴¹ showed an 80% event-free survival rate in patients receiving ATO during consolidation (compared with 63% in the non-ATO control group); 15% of patients were older than 60 years. The optimal number of ATO-based treatments necessary to cure patients with a lower risk of relapse (early molecular complete remission and initial WBC below 10,000 mL) is controversial. The slope of the *PML-RARα* transcript reduction may be one the element of choice in that setting, sparing the use of multiple consolidation cycles in patients with negative PCR after induction. Ongoing trials, including the European group APL2006 trial, are directly comparing ATO-based therapy with more conventional approaches. The ATO-specific supportive care recommendations described earlier also apply for its use as a consolidation therapy.

Finally, encouraging results with a “no-chemotherapy” approach using ATRA and ATO induction (with the use of gemtuzumab or idarubicin when necessary for cytoreduction) followed by alternating cycles of ATRA and ATO have suggested a similar disease-free survival. However, this approach has not been tested in a multi-institutional trial.³⁵

Maintenance

The role of maintenance therapy will be refined in the next years. The APL 93 European study concluded that maintenance therapy for 2 years using sequences of ATRA with or without oral chemo-therapy led to improved relapse-free survival. The GIMEMA study has not confirmed this finding, but final results are still pending.⁴² If patients are molecularly negative at the end of consolidation, the benefit of maintenance therapy may be limited.⁴³ The issue of maintenance has not been addressed specifically for older patients, but accumulation of drugs and the duration of treatment (usually 12–24 months) may have a significant impact on their quality of life.

Relapse

With the inclusion of ATO in primary APL management, relapse is becoming more rare. Retreatment with ATO⁴⁴ or ATRA may be possible, and ATO can cross the central nervous system barrier. Other forms of retinoic acid, such as tamibarotene,⁴⁵ liposomal ATRA,⁴⁶ or gemtuzumab⁴⁷; autologous transplantation for some patients; or new molecules such as histone deacetylase inhibitors⁴⁸ may also be used.

Conclusions

Although outcomes of APL therapy in older patients are inferior to those in younger patients, these relate primarily to problems of toxicity. Alternative and less-toxic strategies using ATO as the foundation of induction or consolidation therapies may improve outcomes and allow older patients previously considered unfit for curative therapy to undergo treatment. Significant work is still needed to define the optimal regimens based on disease risk status and patient comorbidities. APL has the potential to become the first leukemia with no age discrimination in terms of cure rate.

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Figure 1.

Frontline Treatment Strategy Proposal for Older Patients With Acute Promyelocytic Leukemia.

*ATRA should be started because APL is suspected.

†EKG and biochemistry panel, including K⁺, Mg⁺⁺, and Ca⁺, should be monitored twice a week during ATO use.

‡6MP and MTX should be monitored to avoid excessive haematological and liver toxicities. 6MP, 6-mercaptopurine; ATRA, all-trans retinoic acid; ATO, arsenic trioxide; CR, complete remission; DXM, dexamethasone; HU, hydroxyurea; MTX, methotrexate.

Table 1**Treatment Regimens for Older Patients With Acute Promyelocytic Leukemia**

Reference	N	Treatment Plan	CR Rate	Survival
<i>ATRA Plus Chemotherapy</i>				
Kantarjian, 1995	17	ATRA +/- DNR AraC	76%	NR
Burnett, 1999	29	ATRA + anthracycline AraC [*]	73%	NR
Mandelli, 2003	134	ATRA + IDA	86%	OS 81% at 3 y
Sanz, 2004	104	ATRA + IDA	84%	DFS 79% at 6 years
Ades, 2005	129	ATRA +/- DNR AraC	86%	OS 58% at 4 y
Tsimberidou, 2006	36	ATRA + chemotherapy	64%	OS 44% at 4 y
Ferrara, 2010	23	ATRA + IDA	74%	OS 52% at 5 y
<i>ATO</i>				
Shen, 2004 [†]	21	ATRA + ATO	95%	DFS 100% at 2 y
Hu, 2009	14	ATRA + ATO	86%	OS 86% at 5 y
Ravandi, 2009	23	ATRA + ATO +/- GO	83%	OS 74% at 3 y
Dai, 2009 [†]	90	ATRA + ATO	92%	DFS 93% at

Abbreviations: AraC, cytarabine; ATO, arsenic trioxide; ATRA: all-trans-retinoic acid; DFS, disease-free survival; DNR, daunorubicin; IDA, idarubicin; OS, overall survival.

^{*} This study used different combination of anthracyclines plus cytarabine regimens.

[†] The related study includes older patients but does not report specific outcome.