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GUIDELINE

JSH practical guidelines for hematological malignancies, 2023: leukemia-2—acute promyelocytic leukemia (APL)

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Overview

Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia (AML) and referred to as APL with recurrent genetic abnormality *PML::RARA* in the 2017 WHO classification.[1] The cytogenetic abnormality t(15;17)(q24.1;q21.2) is typically observed. Bone marrow generally exhibits neoplastic proliferation of abnormal promyelocytes with abundant azurophil granules, bundles of Auer rods (faggot cells), and nuclear irregularities, but there is also a microgranular variant with fine (few) granules. APL cells, even those of the microgranular variant, stain strongly positive for peroxidase and are often positive for CD13 and CD33, and negative for HLA-DR and CD34 surface markers. APL is characterized by anemia, infection, and hemorrhage due to suppression of normal hematopoiesis, as well as a strong bleeding tendency due to hyperfibrinolytic disseminated intravascular coagulation (DIC) caused by APL cells. APL accounts for 10–15% of AML cases, occurring most commonly in people in their 30–50s and less commonly in people aged 60 years and older.

There is also a rare type of APL with variant *RARA* translocations, in which *PML::RARA* is not detected.[1] The most frequent subtype (approximately 0.8% of APL cases) is t(11;17)/*PLZF*(*ZBTB16*)*::RARA*, and it is important to note that both all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) are ineffective for this subtype as well as the subtype with t(17;17)/*STAT5B::RARA*.[2] All variant *RARA* translocations involve translocation of a certain gene to *RARA* on chromosome 17, which causes fluorescence in situ hybridization (FISH) to show no *PML::RARA* fusion signal but an abnormal number of *RARA* signals. Early detection of the t(15;17) cytogenetic abnormality and the *PML::RARA* fusion gene by FISH or reverse transcription polymerase chain reaction (RT-PCR) is critical to the diagnosis of APL.

Other genetic abnormalities besides the t(15;17) cytogenetic abnormality are required for APL to develop. Comprehensive mutational analysis of APL cells at diagnosis has detected *FLT3*-ITD and -TKD mutations, as well as other mutations including *WT1*, *NRAS*, *KRAS*, *ARID1A*, and *ARID1B*.[3] It is believed that these mutations, most of which activate signal transduction pathways, contribute to APL development coordinating with *PML::RARA*. Abnormalities in the genes which are commonly mutated in other forms of AML (e.g., *DNMT3A*, *NPM1*, *TET2*, *ASXL1*, and *IDH1/2*) are uncommon in APL.

ATRA plus anthracycline-based anti-cancer therapy, which is the standard treatment for previously untreated APL in Japan, provides complete remission (CR) rate in excess of 90% and long-term survival rate of nearly 80% in patients aged 70 years and younger.[4] The issues to address in APL treatment are prevention of early death by DIC and APL differentiation syndrome (DS), and to establish treatments for high-risk patients, such as those with baseline WBC counts ≥ 10,000/μL. In the Japan Adult Leukemia Study Group (JALSG) APL204 study, the early death rate (percentage of patients who died within 30 days of starting initial induction therapy) was approximately 5%, and the majority of these deaths were due to hemorrhagic complications or DS.[5] In induction therapy for APL, ATRA should be started immediately to prevent serious organ hemorrhage due to DIC, and blood transfusions should be used to maintain platelet and fibrinogen levels. Management of DS requires early intervention as soon as DS is suspected due

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to observation of even one sign or symptom, such as fever, dyspnea, or pleural effusion.

Baseline WBC count is the prognostic factor for disease-free survival (DFS) in APL.[6,7] The Sanz risk model classifies a baseline WBC count > 10,000/μL as high risk, WBC count ≤ 10,000/μL with platelet count ≤ 40,000/μL as intermediate risk, and WBC count ≤ 10,000/μL with platelet count > 40,000/μL as low risk,[7] and treatment is generally stratified for high-risk and standard- (low and intermediate) risk groups.

FLT3-ITD is detected in 12–38% of APL cases.[8] Many studies have reported that *FLT3*-ITD is associated with high WBC count, but there is no consensus regarding its prognosis. However, in a meta-analysis of 24 studies, Picharski et al. found that *FLT3*-ITD and -TKD are associated with poor prognosis.[9] In addition, two retrospective studies showed that an *FLT3*-ITD/wild-type ratios of 0.66 (German study)[10] and ≥ 0.5 (Spanish PETHEMA study)[11] are associated with poor outcomes, including relapse-free survival (RFS).

Positivity of CD56 (cutoff of ≥ 10%) is observed in 10–15% of APL cases and is an unfavorable risk factor for relapse independent of WBC count.[12]

APL can also be therapy related, developing after treatment for another cancer. According to a review article, past treatment with a topoisomerase II inhibitor or radiotherapy are risk factors for therapy-related APL. As the remission rate for therapy-related APL is comparable to that for de novo APL, it should be treated using similar regimens used for de novo APL with consideration to factors such as cardiotoxicity and effects of prior treatments.[13]

PML::RARA transcripts in bone marrow cells are useful for assessment of molecular remission. Half of all patients still have the transcripts upon achievement of hematological remission, but must test negative by the end of consolidation therapy. Reappearance of the transcripts during follow-up indicates molecular relapse, and it is recommended to promptly restart treatment in those patients.

The standard treatment for standard-risk APL in Europe and the United States is ATRA plus ATO (this is not covered by Japanese National Health Insurance [NHI]).[14,15] ATO coordinates with ATRA to efficiently induce apoptosis in APL cells with relatively mild toxicity including myelosuppression, giving it superior efficacy and safety to ATRA plus chemotherapy, which is the current standard of care for APL in Japan.

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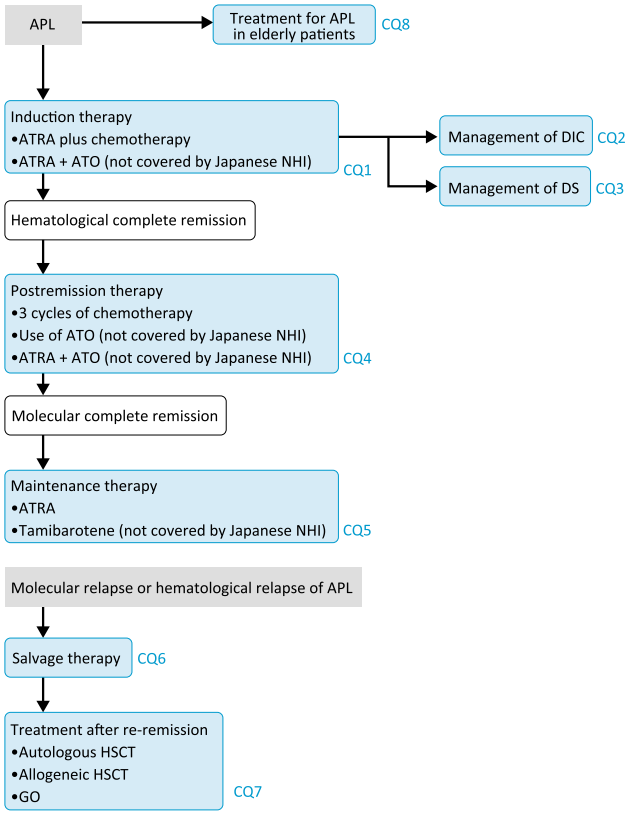
Algorithm



ATRA plus chemotherapy is the standard induction therapy (CQ1) for newly diagnosed APL. Resistance to initial induction therapy is rare, and early death from complications such as serious DIC-induced hemorrhage and DS is the main cause of failure to achieve remission. Therefore, management of DIC (CQ2) and DS (CQ3) is critical in the treatment of APL.

Once hematological remission is achieved, 3 cycles of postremission chemotherapy (CQ4) are performed with the aim of achieving molecular remission, which is evidenced by a negative real-time quantitative PCR result for *PML::RARA* in bone marrow cells. Various approaches including combination regimens with ATRA and use of ATO have been attempted as postremission therapy.

Maintenance combination chemotherapy (CQ5) does not improve outcomes. A study comparing tamibarotene and ATRA for maintenance therapy found that tamibarotene was better in high-risk patients.

Many different regimens from induction to maintenance have been investigated in clinical studies, but obtained treatment outcomes are based on the individual study's entire treatment protocol spanning all phases from induction to maintenance, making it difficult to compare maintenance regimens or consider them in isolation from other treatment phases. Before starting induction therapy, APL risk and comorbidities should be evaluated and an appropriate treatment protocol considering not only induction but also consolidation and maintenance should be determined. Combination of different protocols for induction, consolidation, and maintenance should generally be avoided.

The treatment of choice for relapsed APL (CQ6) is ATO. As hematological relapse is frequently complicated by DIC-induced hemorrhage and DS, it is best to start treatment immediately after detecting molecular relapse by a positive *PML::RARA* result. After reinduction of remission (CQ7), it is recommended to perform ATO-based postremission therapy, followed by allogeneic hematopoietic stem-cell transplantation (HSCT) if *PML::RARA* is detected in bone marrow or high-dose anti-cancer therapy plus autologous peripheral blood stem cell transplantation if it is not detected. If transplantation is not indicated, ATO-based postremission therapy or gemtuzumab ozogamicin (GO), which is also effective for patients who have relapsed after ATO-based treatment, is recommended.

Treatment for elderly patients (CQ8) will also be discussed below.

CQ 1 What induction therapy regimens are recommended for newly diagnosed APL?

Recommendation grade: Category 1
ATRA plus anthracycline-based chemotherapy is recommended

Recommendation grade: Category 1
ATRA plus ATO is more effective than ATRA plus chemotherapy but is not covered by Japanese NHI

Explanation

In the treatment for APL, ATRA, a differentiation-inducing therapeutic agent, is extremely effective. Many studies have demonstrated the efficacy of ATRA plus anthracycline-based chemotherapy. In the Italian AIDA0493 trial, ATRA plus idarubicin (AIDA therapy) yielded a 95% CR rate in patients with newly diagnosed APL.[1] The European APL2000 trial compared ATRA plus daunorubicin against ATRA plus daunorubicin and cytarabine (cytarabine group) as induction therapy in patients with WBC counts less than 10,000/μL

(low and intermediate risk), and found no significant difference in CR rate but better 2-year OS rate in the cytarabine group. However, the cytarabine group also received cytarabine for consolidation.[2]

In the JALSG APL97 study, patients underwent induction with ATRA plus chemotherapy (idarubicin + cytarabine), with the chemotherapy dose adjusted according to risk stratified based on baseline WBC count and peripheral blood APL cell count (myeloblast count + promyelocyte count). Outcomes were favorable, with the overall CR rate at 94% and 6-year OS rate at 83.9%.[3] In the APL204 study, which used a slightly higher cytarabine dose and similar risk stratification, the overall CR rate was 92.7% and 4-year OS rate was 89%.[4]

In summary, ATRA plus anthracycline-based chemotherapy can be expected to achieve CR in over 90% of patients with newly diagnosed APL. The APL204 protocol in particular has excellent reported outcomes in Japanese patients and can be considered the current standard of care in Japan. However, in the APL204 study, the CR and survival rates were suboptimal in patients with identified as high risk in the pretreatment evaluation and patients with leukocytosis during treatment,[4] so treatment approaches for such high-risk patient groups remain to be determined.

Like ATRA, ATO induces differentiation and has been used as single-agent therapy for relapsed APL, even in Japan. However, in various other countries, combination therapy with ATRA + ATO has been developed for newly diagnosed APL and has become the new standard treatment replacing ATRA plus chemotherapy. A unique characteristic of ATRA + ATO is that only these two agents are used even in postremission therapy, with chemotherapy drugs rarely used. The APL0406 trial compared ATRA + ATO with the AIDA regimen for low- and intermediate-risk APL.[5] CR rates were favorable for both treatments and did not differ. Adverse event analysis showed that the AIDA group had significantly higher rates of cytopenia and febrile neutropenia, as well as 4 early deaths. In contrast, the ATRA + ATO group had higher rates of hepatic toxicity (40%) and QTc prolongation (8.5%), but no early deaths. ATRA + ATO yielded a significantly higher 50-month event-free survival (EFS) rate (97.3% vs. 80.0%) and 50-month OS rate (99.2% vs. 92.6%), demonstrating that this combination is not only very safe but also very effective. Some studies of ATRA + ATO in the UK and US included high-risk patients.[6,7] It should be noted that the protocols involved addition of GO to ATRA + ATO during the induction phase for high-risk patients, but both studies showed ATRA + ATO to have high efficacy. These findings established ATRA + ATO as the standard of care for low- and intermediate-risk APL outside of Japan and led to its recommendation as the standard of care for high-risk patients as well. ATO is not currently covered by Japanese NHI for newly diagnosed APL, but ATRA + ATO will hopefully become covered soon.

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CQ 2 What approaches are recommended for management of DIC during induction therapy for newly diagnosed APL?

Recommendation grade: Category 1

Treatment with ATRA should be started immediately without waiting for *PML::RARA* results when a diagnosis of APL is clinically suspected

Recommendation grade: Category 2A

Platelet transfusions to maintain platelet count at 30,000 to 50,000/μL or higher and replacement therapy with fresh frozen plasma to maintain fibrinogen at 150 mg/dL or higher are recommended to prevent hemorrhage during induction therapy

Recommendation grade: Category 2B
Treatment with recombinant thrombomodulin is recommended

Explanation

In APL, tissue factors and cancer procoagulants in APL cells activate the extrinsic coagulation pathway, and high expression of annexin II on the cell surface simultaneously activates fibrinolysis. As a result, hyperfibrinolytic DIC with a strong bleeding tendency occurs.

The great majority of early deaths of newly diagnosed APL patients treated with induction therapy are due to organ hemorrhage, including DIC-induced cerebral hemorrhage.[1,2] When DIC develops during induction therapy, complete blood counts and coagulation markers (prothrombin time, activated partial thromboplastin time, fibrinogen, fibrin/fibrinogen degradation products) should be measured daily until normalization.

ATRA corrects coagulopathy in APL by alleviating hypercoagulability through suppression of tissue factor expression in APL cells, while also suppressing the abnormally enhanced fibrinolytic system by reducing annexin II expression. One strategy for preventing hemorrhage is to promptly start ATRA-based treatment without waiting for *PML::RARA* genetic abnormality results when clinical findings are suggestive of APL.[3]

In a retrospective analysis of JALSG APL studies, high-risk factors for severe bleeding included hypofibrinogenemia (< 100 mg/dL), high WBC count (> 20,000/μL), and low platelet count (< 30,000/μL).[1,2] Therefore, platelet transfusions to maintain platelet count at 30,000–50,000/μL or higher and replacement therapy with fresh frozen plasma to maintain fibrinogen at 150 mg/dL or higher are recommended to prevent bleeding.

A retrospective analysis comparing platelet and fibrinogen replacement alone, anticoagulant therapy with heparin, and antifibrinolytic therapy with drugs such as tranexamic acid for prevention of organ hemorrhage, which was conducted during the time period before the introduction of ATRA when APL was treated with chemotherapy alone, showed no differences in remission rates or the early mortality from hemorrhage.[4] Use of tranexamic acid is not recommended. The Spanish PETHEMA group showed that combination of tranexamic acid with ATRA increased the risk of thrombosis.[5] Use of heparins such as low-molecular-weight heparin and danaparoid is not currently recommended because the increased risk of hemorrhagic adverse reactions outweighs the benefit for correcting hypercoagulability.[6]

No study has demonstrated a clear benefit from anticoagulant therapy with synthetic protease inhibitors such as gabexate mesilate or nafamostat mesilate.

Recombinant thrombomodulin is widely used to treat APL-induced DIC in practice in Japan. According to the post-marketing all-case surveillance report of treatment for 172 cases of APL-induced DIC, the rate of early mortality due to hemorrhage within the first 30 days was a relatively low 3.5%.[7] Recombinant thrombomodulin reduces expression of annexin II on the surface of APL cells and activates protein C in the presence of thrombin, which suppresses the coagulation, and is therefore a logical choice for treating APL-induced DIC. A small retrospective study reported that recombinant thrombomodulin resolved DIC more rapidly and reduced transfusion volume compared with historical controls.[8]

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CQ3 What treatments are recommended for DS?

Recommendation grade: Category 2A
It is recommended to detect DS early and start dexamethasone as soon as DS is suspected

Recommendation grade: Category 2A
In severe cases of DS, ATRA and ATO should be discontinued

Explanation

DS is a major complication that occurs when ATRA or ATO induces APL cell differentiation during induction therapy for APL and can be fatal when severe. Signs and symptoms used to diagnose DS are (1) dyspnea, (2) unexplained fever, (3) weight gain ≥ 5 kg, (4) unexplained hypotension, (5) acute renal failure, (6) pulmonary infiltrates, and (7) pleuropericardial effusion. DS is classified as moderate when 2 or 3 of these are present and severe when 4 or more are present.[1] Although one sign or symptom alone is insufficient to definitively diagnose DS, it is important to take appropriate measures at this stage of suspected DS. In an analysis of patients treated with ATRA plus chemotherapy, the incidence of DS ranged from 15 to 25%, with bimodal peaks for the first week and days 15–28.[1] Risk factors include high baseline WBC count, increased WBC count during treatment, and high body mass index or body surface area.[2–4]

The APL93 trial showed that starting ATRA and chemotherapy simultaneously may reduce the incidence of DS compared with starting chemotherapy after ATRA.[5] In the Intergroup 0129 study, patients receiving single-agent ATRA induction therapy were given additional hydroxyurea when their WBC count increased, but the incidence of DS was high at 26%, and DS sometimes recurred after resumption of ATRA.[6] Based on these results and the pathology of DS, chemotherapy to reduce WBC count can be considered effective in prevention of DS.

Steroid prophylaxis is also used to suppress onset of DS. One study compared two protocols for the AIDA regimen: the LPA96 trial, where only patients with a baseline WBC count > 5000/μL were given dexamethasone, and the LPA99 trial, where all patients were given prednisolone prophylaxis.[1] Treatment per the LPA96 protocol was a risk factor for severe DS, suggesting that universal prednisolone prophylaxis for DS may be effective. In the European APL2000 trial, dexamethasone was only given to patients whose WBC count was > 10,000/μL before or during treatment,[7] and in the Japanese APL204 study, steroid prophylaxis was not given but high WBC counts before and during treatment were managed with chemotherapy.[2] Although the significance of steroid prophylaxis is unclear due to the lack of a significant difference in DS incidence between these studies as well as differences in patient characteristics (e.g., chemotherapy received), it merits consideration in patients with a high WBC count.[8] Caution must be taken for treatment with ATRA + ATO because both ATRA and ATO strongly induce differentiation but the regimen does not include chemotherapy. In the APL0406 trial, increases in WBC count were significantly more frequent in the ATRA + ATO group than the AIDA group (47% vs. 24%).[9] All patients received prednisolone prophylaxis and any increases in WBC count were managed by administration of hydroxyurea at a dose of up to 4000 mg/day, leading to no difference in the incidence of moderate to severe DS (note that the approved dose of hydroxyurea in Japan is up to 2000 mg/day).

To treat DS, it is critical to start intravenous administration of dexamethasone 10 mg twice daily as soon as DS is suspected.[8] Although other conditions such as infection or heart failure can produce the similar signs and symptoms used to diagnose DS, the European LeukemiaNet (ELN) expert panel recommendations strongly recommend immediate treatment with dexamethasone even in such cases.[8] Treatment with ATRA or ATO should be interrupted in severe cases of DS. Once DS is resolving, dexamethasone should be tapered off, and if treatment with ATRA or ATO was interrupted, ATRA or ATO should be resumed only after complete resolution of DS symptoms.

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CQ4 What postremission therapy is recommended for newly diagnosed APL after induction of remission with ATRA plus chemotherapy?

Recommendation grade: Category 1
Three cycles of anthracycline and cytarabine combination therapy is recommended

Explanation

The postremission therapy phase for newly diagnosed APL treated with ATRA plus chemotherapy is divided into two sub-phases: short-term consolidation therapy, followed by longer-term maintenance therapy. This section discusses consolidation therapy. In the JALSG APL204 study, induction therapy consisting of ATRA, idarubicin, and cytarabine with risk-stratified doses was followed by consolidation therapy with 3 cycles of anthracycline plus cytarabine, and the 7-year OS rate was a favorable 87%.[1]

In the AIDA0493 trial, patients received the AIDA regimen for induction followed by 3 cycles of consolidation with an anthracycline plus cytarabine or etoposide.[2] In the AIDA2000 trial, low- and intermediate-risk patients received 3 cycles of ATRA plus an anthracycline, and high-risk patients received 3 cycles of the same drugs plus cytarabine as a consolidation.[2] The fact that OS in low- and intermediate-risk patients did not differ between the both studies and high-risk patients had better outcomes with the AIDA2000 protocol suggests that addition of cytarabine is beneficial, particularly for high-risk patients.[2]

In summary, protocols for consolidation after induction with ATRA plus chemotherapy use 3 cycles of anthracycline-based treatment with cytarabine or ATRA added. Although treatment outcomes do not differ greatly and consolidation regimens cannot be compared in isolation from other treatment phases, the standard of care in Japan is the JALSG APL204 protocol evaluated in Japanese patients, and the recommended consolidation regimen is 3 cycles of anthracycline and cytarabine combination therapy per that protocol.

ATRA + ATO is the standard therapy outside Japan, but Japanese NHI does not cover ATO for newly diagnosed APL. With ATRA + ATO, patients receive only ATRA and ATO for both induction and postremission therapy. In one representative trial, APL0406, patients received 7 cycles of ATRA, with 1 cycle consisting of 2 consecutive weeks of ATRA administration followed by a 2-week rest period, along with 4 cycles of ATO, with 1 cycle consisting of 4 weeks of ATO administration 5 days per week followed by a 4-week rest period.[3] ATRA and ATO are administered in parallel, so 2 cycles of ATRA are given for each cycle of ATO.

ATO may also be effective as postremission therapy after induction with ATRA plus chemotherapy. In the North American C9710 trial, where one group of patients was treated with induction with ATRA, daunorubicin, and cytarabine and subsequent 2 cycles of postremission therapy with ATRA plus daunorubicin, and another group was treated with the same protocol plus an additional 2 cycles of single-agent ATO before the 2 cycles of postremission therapy, addition of 2 cycles of ATO improved 3-year EFS rate (80% vs. 63%).[4] Another study conducted in the United States investigated reducing the dose of chemotherapy drugs by limiting postremission therapy to 1 cycle of ATRA/daunorubicin/ATO combination therapy.[5] In summary, incorporation of ATO into postremission therapy after induction therapy with ATRA plus chemotherapy is expected to enhance efficacy and safety.

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CQ5 What maintenance therapy regimen is recommended for newly diagnosed APL in molecular remission?

Recommendation grade: Category 2B
ATRA- or tamibarotene-based maintenance therapy can be considered for high-risk patients

Explanation

The postremission therapy phase for newly diagnosed APL treated with ATRA plus chemotherapy is divided into two sub-phases: short-term consolidation therapy, followed by longer-term maintenance therapy. Some research has examined the significance of maintenance therapy, particularly in patients in molecular remission after consolidation therapy. The JALSG APL97 study, which was conducted in patients in molecular remission after completion of consolidation therapy, compared intensified maintenance with 6 cycles of anthracycline-based combination chemotherapy against observation, and found that 6-year OS was significantly worse in the intensified maintenance group.[1] Based on these results, intensified maintenance therapy for patients in molecular remission is not recommended.

The Italian AIDA0493 trial compared single-agent ATRA, ATRA + methotrexate + mercaptopurine, methotrexate + mercaptopurine, and no maintenance therapy, and found no significant difference in 12-year DFS rate between the four groups.[2] The French APL93 trial also compared the same four groups, and found that 10-year cumulative incidence of relapse (CIR) was highest in the group that received no maintenance therapy and lowest in the group that received ATRA + methotrexate + mercaptopurine.[3] Maintenance therapy was particularly effective in patients whose baseline WBC count was > 5,000 /μL. The JALSG APL204 study compared maintenance therapy with single-agent ATRA versus single-agent tamibarotene.[4] Tamibarotene, a synthetic retinoid, is a more potent inducer of APL cell differentiation than ATRA but is not covered by Japanese NHI for newly diagnosed APL. RFS did not differ between the two groups among low- and intermediate-risk patients, but was significantly longer with tamibarotene in high-risk patients with a baseline WBC count ≥ 10,000/μL. Although these studies do not show a clear benefit to maintenance therapy in low- and intermediate-risk patients, it is more beneficial in patients with a higher baseline WBC count. Consequently, maintenance therapy with single-agent ATRA, ATRA + methotrexate + mercaptopurine, or single-agent tamibarotene may be considered for high-risk patients.

The ATRA + ATO regimen currently used as the standard therapy outside Japan consists of 7 cycles of ATRA and 4 cycles of ATO as postremission therapy, with no subsequent maintenance therapy.[5]

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CQ 6 What is the optimal reinduction therapy regimen for relapsed APL?

Recommendation grade: Category 1
Regimens that include ATO are recommended for reinduction after relapse of APL

Recommendation grade: Category 2B
Regimens that include GO or tamibarotene should be considered for patients refractory or intolerant to ATO

Explanation

Combination of ATRA with chemotherapy has improved treatment outcomes for APL, but relapse still occurs in approximately 15–20% of patients, most often within 3 years of complete remission. Essential factors to consider when selecting reinduction therapy for relapsed APL are the initial treatment regimen, whether the relapse occurred during treatment, and the duration of remission before relapse.

When relapse has occurred after initial treatment with ATRA plus chemotherapy, second molecular remission can be achieved with single-agent ATO in 80–90% of patients.[1,2] In the JALSG APL205R study, autologous HSCT after induction therapy with ATO for relapsed APL yielded a CR rate of 81%.[3] ATO-based regimens even yield a high second remission rate in patients who initially received ATO-based therapy.[4] The significance of ATO + ATRA combination therapy for relapse after initial treatment with ATRA is

unclear; a small randomized controlled trial showed no difference in CR rate or survival between single-agent ATO and ATO + ATRA.[5] Anthracycline combination chemotherapy is also an option for early relapse after initial treatment with ATRA + ATO.

Another option with proven efficacy besides ATO is GO. When 16 patients in molecular relapse received single-agent therapy with GO, 9 of the 11 patients evaluated for measurable residual disease (MRD) after the second dose of GO achieved second molecular remission.[6] However, use of GO should be avoided or transplantation should be delayed in patients scheduled for HSCT because GO may increase the risk of hepatic sinusoidal obstruction syndrome after allogeneic HSCT. The synthetic retinoid tamibarotene is another option for relapsed patients: single-agent tamibarotene achieved remission in 58% of patients in relapse after treatment with ATRA in a phase II study.[7] Among 14 patients who relapsed after ATRA + ATO therapy, the overall response rate with single-agent tamibarotene was 64%, the cytogenetic remission rate was 43%, and the molecular remission rate was 21%, but the response was not durable (median EFS 3.5 months, median OS 9.5 months).[8]

Central nervous system (CNS) involvement has been reported in 2–5% of patients with relapsed APL, so attention needs to be paid to CNS involvement. A study by the European APL Group reported CNS involvement in 5.3% of patients with relapse after ATRA plus chemotherapy and identified WBC ≥ 10,000/μL at diagnosis as a risk factor for CNS involvement.[9] CNS relapse is treated by once- to twice-weekly intrathecal injections of methotrexate, cytarabine, and hydrocortisone until disappearance of blasts in cerebrospinal fluid, followed by periodic intrathecal injections thereafter.

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CQ 7 What postremission therapy is recommended for APL in second remission?

Recommendation grade: Category 2A

Autologous transplantation is recommended if MRD is not detected after postremission therapy with ATO

Recommendation grade: Category 2A

Allogeneic HSCT is recommended for transplantation-eligible patients with MRD detected

Explanation

Autologous or allogeneic HSCT in second CR of APL has been shown to improve survival, particularly OS. Before ATO became available, reinduction therapy for relapsed patients was performed with ATRA plus chemotherapy. The APL91 and APL93 trials of the European APL Group, which compared autologous and allogeneic HSCT in second CR after the reinduction therapy, found that autologous HSCT yielded a superior 7-year OS rate to allogeneic HSCT and to no transplantation (59.8% vs. 51.8%, 39.5%). Allogeneic HSCT yielded the best RFS rate (92.3% vs. 79.4%, 38%), but treatment-related mortality was only 6% with autologous HSCT versus 39% with allogeneic HSCT.[1] In addition, an analysis ($n = 625$) by the European Group for Blood and Marrow Transplantation showed that the 5-year DFS rate for patients in second CR was 51% for autologous HSCT and 59% for allogeneic HSCT.[2] Even studies conducted after ATO therapy for relapsed patients became

available have demonstrated the efficacy of HSCT in second CR. In an Indian study where patients with relapsed APL underwent reinduction therapy with single-agent ATO or ATRA + ATO, the 5-year EFS rate was significantly better in patients who underwent autologous HSCT after reinduction than those who did not undergo HSCT (83.3% vs. 34.5%).[3] An ELN registry study compared 93 patients who underwent autologous or allogeneic HSCT after ATO-based reinduction and postremission therapy against 55 patients who did not undergo HSCT. The HSCT group had a better 3-year OS rate (80% vs. 59%, $p = 0.03$) and 3-year CIR (35% vs. 58%, $p = 0.02$), and neither OS nor CIR differed significantly between the 60 patients in the autologous HSCT group and 33 patients in the allogeneic HSCT group.[4]

In the JALSG APL205R study, autologous HSCT was performed in patients who were MRD-negative by quantitative RT-PCR after reinduction and postremission therapy with ATO for APL relapsed on an ATRA plus chemotherapy regimen. The CR rate was 81%, 5-year EFS rate was 65%, and 5-year OS rate was 77%.[5] In addition, outcomes of autologous HSCT in second CR have improved since ATO became available for relapsed APL.[6] The recommended approach for patients in second CR of APL is postremission therapy with ATO, along with autologous HSCT if the patient is MRD-negative and transplant-eligible. Allogeneic HSCT has higher treatment-related mortality than autologous HSCT, and thus is only recommended in a limited group of patients based on MRD status in remission and time to relapse. However, a Japanese registry study showed that MRD status before autologous HSCT is not a prognostic factor, so autologous HSCT may be an option when allogeneic HSCT is not feasible.[7]

Some recent studies have questioned the necessity of autologous HSCT for relapsed APL because some patients achieve good outcomes with ATO-based chemotherapy alone, but this must be verified in a prospective study. In a long-term follow-up report from the National Cancer Research Institute AML17 trial in the United Kingdom, 18 patients who relapsed with non-CNS involvement after initial treatment with the AIDA regimen did not undergo HSCT after ATRA + ATO therapy, and 14 of those patients maintained molecular remission.[8] GO is recommended for transplant-ineligible patients who are refractory or intolerant to ATO.[9]

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CQ 8 What is the optimal treatment approach for APL in elderly patients?

Recommendation grade: Category 2A

Although it is equally appropriate to aim for curative treatment in elderly patients with relatively good performance status as in younger patients, treatment intensity (e.g., anthracycline dose) should be lower than that for younger patients

Recommendation grade: Category 2A

Use of an ATO-based regimen is also reasonable in elderly patients for whom maintenance of treatment intensity would be impractical due to serious comorbidities or other reasons (not covered by Japanese NHI)

Explanation

Although treatment of APL in elderly patients poses some challenges such as adverse events due to treatment toxicity and maintenance of treatment intensity, reduced-intensity treatment with ATRA plus chemotherapy has improved outcomes, and regimens including ATO (not covered by Japanese NHI) have been demonstrated as effective.

In LPA96 and LPA99 trials, conducted by the Spanish PETHEMA group, APL patients received induction therapy with ATRA plus idarubicin followed by anthracycline-based postremission therapy with no adjustment for age. An analysis of patients aged 60 years and older in these two trials showed a favorable CR rate but a high rate of early death by infection in elderly patients.[1] Compared with the LPA2005 trial, where treatment was adjusted by age, 5-year DFS rate was 69% for LPA96/99 versus 87% for LPA2005 ($p=0.04$), and 5-year OS rate was 60% versus 74% ($p=0.06$), indicating that use of a risk- and age-adjusted protocol for ATRA plus chemotherapy improves outcomes in APL patients aged 60 years and older.[2] The standard AIDA regimen consists of 3 cycles, but studies by the Italian GIMEMA group and the German Study Alliance Leukemia study group showed that age-based reduction of the number of AIDA cycles in postremission therapy reduced the rate of treatment-related adverse events while achieving comparable outcomes.[3,4].

ATO causes few age-dependent adverse reactions and is expected to be effective in elderly patients with APL. The North American C9710 trial showed that addition of single-agent ATO postremission therapy significantly improved survival outcomes in elderly patients aged 61–79 years.[5] A group from M.D. Anderson Cancer Center investigated combination therapy with ATO and ATRA for induction and postremission therapies and obtained favorable results in patients aged 60 years and older.[6] A retrospective international collaborative study in 433 patients aged 70 years and older with newly diagnosed APL that compared ATRA plus chemotherapy against ATRA + ATO (± chemotherapy) showed that ATRA + ATO is well tolerated in elderly APL patients (≥ 70 years), and is particularly beneficial for those in the high-risk group.[7] In summary, ATO-based therapy is a reasonable choice for elderly patients because it is associated with fewer fatal adverse events than typical chemotherapy, although ATO is not covered by Japanese NHI for newly diagnosed APL as of May 2023.

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Name (affiliation)			Conflict of interest category				
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