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Special Report

Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the European LeukemiaNet

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Since the comprehensive recommendations for the management of acute promyelocytic leukemia (APL) reported in 2009, several studies have provided important insights, particularly regarding the role of arsenic trioxide (ATO) in frontline therapy. Ten years later, a European LeukemiaNet expert panel has reviewed the recent advances in the management of APL in both frontline and relapse settings in order to develop updated evidence- and expert opinion–based recommendations on the management of this disease. Together with providing current indications on genetic diagnosis, modern risk-adapted frontline therapy, and salvage treatment, the review contains specific recommendations for the identification and management of the most important complications such as the bleeding disorder APL differentiation syndrome, QT prolongation, and other all-*trans* retinoic acid– and ATO-related toxicities, as well as recommendations for molecular assessment of the response to treatment. Finally, the approach to special situations is also discussed, including management of APL in children, elderly patients, and pregnant women. The most important challenges remaining in APL include early death, which still occurs before and during induction therapy, and optimizing treatment in patients with high-risk disease. (*Blood*. 2019;133(15):1630-1643)

Introduction

After the initial therapeutic success reported in 1973 using an anthracycline (daunorubicin),[1] the management and outcome of acute promyelocytic leukemia (APL) has been revolutionized by the introduction of all-*trans* retinoic acid (ATRA; tretinoin) and arsenic trioxide (ATO) in 1988[2] and 1996,[3] respectively. Multicenter studies over the past 3 decades have demonstrated the efficacy of ATRA plus chemotherapy and, subsequently, of ATRA plus ATO, with or without chemotherapy. However, the optimal management of APL also requires early diagnosis, institution of aggressive supportive measures, appropriate management of treatment-related complications, and monitoring of measurable residual disease (MRD).

In 2009, a detailed list of recommendations for the management of APL was reported by an expert panel on behalf of the European LeukemiaNet (ELN).[4] Since then, several studies have provided important insights about frontline therapy. In particular, 2 large randomized trials exploring the role of ATO have established a new standard of care in this setting.[5,6] Based on the results of these studies, both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have recently approved ATO for the treatment of newly diagnosed patients with low-to-intermediate risk APL (defined as white blood cell [WBC] count $\leq 10 \times 10^9$/L). This review will address this and other recent advances in the management of APL in both frontline and relapse settings.

Methods

The panel included 21 members with recognized clinical and research expertise in APL. We identified relevant articles appearing between the publication of the 2009 version of the ELN recommendations[4] and June 2018 by systematically searching and

critically reviewing PubMed, Cochrane, and Medline databases in the English language. The levels of evidence and grading of recommendations were those defined in the "General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine" (Appendix).[7] We emphasize changes based on new data from 2009. Thus, with few exceptions, only articles published after 2009 will be quoted.

The panel acknowledges that drug availability and costs may vary significantly in different parts of the world. Therefore, alternative treatment options will be recommended for patients in countries facing these constraints.

Approach to the patient with suspected APL

To prevent very early deaths occurring prior to treatment, individuals with suspected APL should be immediately hospitalized and managed as a medical emergency. The diagnosis must be confirmed at the genetic level by experienced reference laboratories. However, even before confirmation, ATRA and measures to counteract the coagulopathy should be initiated immediately based solely on the clinical suspicion of APL and review of the peripheral blood (PB) smear (Table 1).

Genetic diagnosis

A rapid confirmation of genetic diagnosis is mandatory and should be performed, if possible, on bone marrow (BM) samples. The identification of the APL-specific genetic lesion can be made by conventional karyotyping, fluorescence in situ hybridization (FISH), reverse transcriptase polymerase chain reaction (RT-PCR; or real-time quantitative PCR [RQ-PCR]), or comparable nucleic acid–based techniques (eg, reverse transcription–quenching loop-mediated isothermal amplification [RT-QLAMP]).[8] The analysis of promyelocytic leukemia (PML) nuclear staining in leukemic cells using anti-PML monoclonal antibodies can be a surrogate for genetic diagnosis. All of these options are equally specific, but not equally sensitive, with cytogenetic analysis most prone to false-negatives. FISH and immunostaining with anti-PML monoclonal antibodies are more rapid and highly sensitive and specific. However, PML nuclear staining relies on subjective interpretation, and, unless performed by experienced examiners, appears less reproducible than the other techniques. These methods cannot substitute for RT-PCR or RQ-PCR, which should always be run in parallel, as the only technique allowing definition of the type of PML/RARA isoform and quantification for subsequent MRD evaluation. Advantages and disadvantages of each technique, as well as recommendations for sample processing and banking, were comprehensively addressed in the previous 2009 ELN recommendations.[4]

The prognostic significance of *FLT3* internal tandem duplications in patients given ATRA plus chemotherapy remains controversial.[9] Recent data indicate that *FLT3* internal tandem duplication mutations do not confer a worse prognosis in patients receiving ATO plus ATRA.[10,11] Similarly, the prognostic significance of other recurrent but infrequent mutations in *WT1*, *NRAS*, and *KRAS* is uncertain and, therefore, their routine detection at diagnosis is not recommended.

Recent studies using next-generation-sequencing approaches have examined the mutational landscape of APL comparing diagnostic and relapse samples. These studies disclosed the presence at diagnosis of several gene mutations in addition to PML/RARA, together with an increased rate of mutations, including point mutations affecting the RARA and/or PML moieties of the hybrid oncoprotein in relapsed samples.[12,13] Such additional aberrations had no impact on prognosis and their detection is therefore not recommended in the routine evaluation of patients outside of clinical trials.

Supportive measures to counteract the coagulopathy

As a consequence of the complex coagulopathy associated with APL, which reflects consumptive coagulation as well as primary and secondary fibrinolysis, intracerebral and pulmonary hemorrhages are the most frequent causes of death both prior to and shortly after treatment initiation. Less commonly, thrombotic complications may dominate the clinical presentation.

The supportive measures recommended to treat the coagulopathy have not changed during the last decade. Platelet counts and routine coagulation parameters, including prothrombin time, activated partial thromboplastin time, and thrombin time, as well as levels of fibrinogen and fibrinogen-fibrin degradation products should be monitored at least daily and more frequently if required. Transfusions of fibrinogen and/or cryoprecipitate, platelets, and fresh-frozen plasma should be given immediately upon suspicion of the diagnosis, and then daily or more than once a day if needed, to maintain the fibrinogen concentration above 100 to 150 mg/dL, the platelet count above 30×10^9/L to 50×10^9/L, and the international normalized ratio (INR) below 1.5. Supportive treatment should be continued during induction therapy until disappearance of all clinical and laboratory signs of the coagulopathy.

The benefit of using heparin, tranexamic acid, or other anticoagulant or antifibrinolytic agents to attenuate the hemorrhagic and thrombotic risk associated with the coagulopathy before and during remission induction therapy remains questionable.

The management of a cerebral stroke or major thrombosis in the context of the coagulopathy remains challenging and potentially threatening with few data available. When a catheter-related thrombosis occurs, and a catheter is in place despite the recommendation against its use in APL, the central venous line should be removed as soon as possible. The use of unfractionated heparin could be considered in case of severe thrombosis, although the risk of hemorrhagic transformation of a stroke warrants considerable caution. If a low-molecular-weight heparin is used, the dose should be adapted to the platelet counts (eg, 70% to 80% if $<70 \times 10^9$/L; 50% if $<50 \times 10^9$/L; stop if $<30 \times 10^9$/L).

Since 2009, there appears to be no additional evidence supporting the use of recombinant factor VIIa to counteract APL-associated bleeding. Recombinant soluble thrombomodulin, an anticoagulant also active against fibrinolysis, inflammation, and endothelial cell damage,[14] has been used for the treatment of disseminated intravascular coagulation in Japan since 2008. A phase 3 trial showed that recombinant thrombomodulin significantly improved disseminated intravascular coagulation associated with hematological malignancies or infections.[15] This was also observed in a large retrospective study[16] and in other

Table 1. Diagnostic workup and supportive care

Recommendation	Level of evidence–grade of recommendation	Changes compared with the 2009 recommendations
1.1. Once a diagnosis of APL is suspected, the disease should be managed as a medical emergency	IV–C	Unchanged
1.2. Patients should be managed by an experienced and multidisciplinary team in centers with rapid access to genetic diagnosis, blood products, and specific drugs, such as ATRA, ATO, and chemotherapy	IV–C	Unchanged
1.3. Diagnosis should be confirmed by molecular detection of *PML-RARA* fusion (or rare molecular variants)	IIa–B	Unchanged
1.4. In addition to FISH, RT-PCR, RQ-PCR, RT-QLAMP, and immunostaining with anti-PML antibody can be used for rapid diagnosis of APL	IIa–B	Updated
Management of coagulopathy		
1.5. Treatment with ATRA should be started immediately when a diagnosis of APL is suspected	Ib–A	Unchanged
1.6. Transfusions of fibrinogen and/or cryoprecipitate, platelets, and fresh-frozen plasma should be given immediately upon suspicion of the diagnosis, and then daily or more than once a day if needed, to maintain the fibrinogen concentration above 100-150 mg/dL, the platelet count above 30×10^9/L to 50×10^9/L, and the INR below 1.5	IIb–B	Slightly modified
1.7. Platelet counts and routine coagulation parameters, prothrombin time, activated partial thromboplastin time, and thrombin time, as well as levels of fibrinogen and fibrinogen-fibrin degradation products, should be monitored at least daily and more frequently if required, until disappearance of all clinical and laboratory signs of the coagulopathy	IIb–B	New recommendation
1.8. The benefit of heparin, tranexamic acid, or other anticoagulant or antifibrinolytic therapy remains questionable and should not be used routinely outside of the context of clinical trials	IV–C	Unchanged
1.9. Central venous catheterization, lumbar puncture, and other invasive procedures (eg, bronchoscopy) should be avoided before and during remission induction therapy due to high risk of hemorrhagic complications	IV–C	Unchanged
Management of hyperleukocytosis (WBC count >10 × 10^9/L) at presentation		
1.10. Cytoreductive chemotherapy should be started without delay, even if the molecular results are still pending: • For patients to be treated with ATRA + chemotherapy, idarubicin or daunorubicin alone or combined with cytarabine should be given • For patients to be treated with ATRA + ATO, cytoreduction can be done with idarubicin (12 mg/m^2) or GO (6-9 mg/m^2)	IV–C	Updated
1.11. Leukapheresis should be avoided due to risk of precipitating fatal hemorrhage	III–B	Unchanged
1.12. Prophylactic corticosteroids can be given, which may reduce the risk of APL differentiation syndrome	IV–C	Unchanged
Management of APL differentiation syndrome		
1.13. Corticosteroids (10 mg of dexamethasone IV twice daily) should be started immediately at the earliest clinical suspicion of incipient APL differentiation syndrome; once the syndrome has resolved, steroids can be discontinued and ATO/ATRA recommenced	IIa–B	Unchanged
1.14. Temporary discontinuation of differentiation therapy (ATRA or ATO) is indicated only in case of severe APL differentiation syndrome	IIa–B	Unchanged

GO, gemtuzumab ozogamicin.

Table 1. (continued)

Recommendation	Level of evidence–grade of recommendation	Changes compared with the 2009 recommendations
Management of treatment with ATO		
1.15. An increase of WBC levels above 10×10^9/L after treatment initiation with ATRA and/or ATO should be interpreted as a sign of ATRA/ATO-induced differentiation and should not lead to reclassification of the patient as having high-risk disease	IV–C	New recommendation
1.16. For patients who develop a significant increase of WBC counts after treatment initiation with ATRA and/or ATO, the addition of hydroxyurea (2 g/d) or, in case of extreme hyperleukocytosis, idarubicin (12 mg/m^2) or GO (6-9 mg/ m^2) can be considered	IV–C	New recommendation
1.17. Treatment with ATO should be restricted to cases confirmed to be *PML/RARA*$^+$	IIb–B	Unchanged
1.18. Treatment with ATO requires careful monitoring to maintain electrolytes in the normal range, keeping the serum potassium above 4.0 mEq/L and serum magnesium above 1.8 mg/dL	IV–C	Unchanged
1.19. Treatment with ATO requires monitoring of the QT/QTc interval at least twice weekly: • For routine ECG surveillance of QT interval prolongation, alternative rate adjustment formulas other than the classical Bazett correction (eg, Fridericia, Hodges, or Sagie/ Framingham) should be used • Patients with episodes of significant QT prolongation or torsades de pointes, with clinical symptoms, such as dizziness and syncope, or with other risk factors should be closely monitored; telemetered ECG monitoring can be strongly considered in some patients at very high risk • If the QT (or QTc for patients with heart rate >60 beats per minute) interval is prolonged longer than 500 ms, ATO should be withheld, the electrolytes repleted (potassium and magnesium), and other medications that may cause prolonged QTc interval sought and possibly discontinued • Once the QT/QTc returns to ~460 ms, and the electrolytes are repleted, ATO may be resumed	IV–C	New recommendation

GO, gemtuzumab ozogamicin.

reported smaller series.[17-19] However, despite these encouraging results, the panel considers that further prospective controlled studies are warranted and, therefore, does not recommend the use of this agent outside of clinical trials.

Invasive procedures such as central venous catheterization, lumbar puncture, and bronchoscopy should be avoided at diagnosis and during initial treatment as long as the coagulopathy is active. These recommendations, provided in an earlier version in the 2009 recommendations, have now been added to Table 1.

Initiation of ATRA

ATRA should be initiated immediately once APL is suspected; if the diagnosis is not supported by genetic or molecular data, ATRA should be discontinued. For patients presenting with low WBC count ($\leq 10 \times 10^9$/L), administration of other antileukemic agents such as ATO or chemotherapy may be delayed until the genetic diagnosis is confirmed; however, in patients with leukocytosis (ie, WBC count $>10 \times 10^9$/L), chemotherapy should be started without delay even if the diagnostic molecular results are still pending. Idarubicin or daunorubicin with cytarabine have been the most common chemotherapy-based approaches, whereas hydroxyurea (2-4 g per day) or 1 to 2 doses of idarubicin (12 mg/m^2) or gemtuzumab ozogamicin (GO; 6-9 mg/m^2, currently off-label) have been the most frequently cytoreductive chemotherapy used when ATO-based approaches are used. Prophylactic corticosteroids to prevent differentiation syndrome have been used in some studies but the value of the use of steroids remains unclear. Although their benefit remains uncertain, prophylactic corticosteroids can be considered in patients with a WBC count $>5 \times 10^9$/L to 10×10^9/L at presentation or in those showing WBC increase after the start of ATRA. Non–high-risk patients whose WBCs frequently increase to a level $>10 \times 10^9$/L after treatment initiation should not be reclassified as high risk because the WBC increase should be interpreted as a result of ATRA-induced differentiation.

Appropriate setting for the management of APL

The panel again recommends that patients with APL be managed by an experienced team in centers with documented rapid access to genetic diagnosis, a broad range of blood products, as

well as ATRA, ATO, and chemotherapy. ATRA, in particular, should be immediately available. The panel strongly recommends that, during induction therapy, all patients, regardless of risk, should be hospitalized to ensure rigorous clinical monitoring and supportive care. However, once induction is advanced and the coagulopathy and other complications are resolved, some patients could be discharged, provided that a rapid rehospitalization is guaranteed if necessary.

Treatment of newly diagnosed patients

Supportive care

Supportive care recommendations have not substantially changed since 2009. Table 1 lists measures to treat coagulopathy and leukocytosis, as well as recommendations for the management of complications typically associated with the administration of ATRA and ATO. Recommendations for prevention and treatment of APL differentiation syndrome, and for maintenance of serum potassium and magnesium levels, remain unchanged. In addition to reiterating the need to avoid the concomitant use of drugs such as ciprofloxacin, fluconazole, and ondansetron among others commonly used in this setting that are known to prolong the corrected QT (QTc) interval,[20] recommendations for QT monitoring have been modified in accordance with an important recent study.[21] Although carried out in patients with non-APL acute myeloid leukemia (AML) and myelodysplastic syndrome treated with ATO combined with low-dose cytarabine, the main conclusions drawn based on extensive electrocardiogram (ECG) data can be extrapolated to the use of ATO in APL. In this study, based on 113 patients treated with ATO, 90% had QTc prolongation >470 milliseconds with 65% above 500 milliseconds when rate correction was performed with the standard Bazett formula, yet none developed severe or clinically relevant arrhythmias.[21] In contrast, the use of alternative rate-correction formulas (Fridericia, Hodges, or Sagie/Framingham) indicated that only 24% to 32% of patients had rate-corrected QT intervals above 500 milliseconds. Thus, use of these formulas will result in a reduction of unnecessary interruptions of ATO therapy.

Strict monitoring for ECG changes, even via a telemetered ECG, is strongly recommended for patients with previous episodes of significant QTc prolongation or torsades de pointes, those with relevant clinical symptoms (such as dizziness and syncope), or those with other risk factors for cardiac arrhythmias.

Patients who reach an absolute QTc interval value longer than 500 milliseconds or those who develop syncope, tachycardia, or arrhythmia should be hospitalized for ECG and electrolyte monitoring, ATO should be temporarily withheld, together with, whenever possible, other medications that may prolong the QTc interval. ATO may be resumed at 50% and later increased to full dose when the QTc returns to ~460 milliseconds, provided that electrolytes are repleted.

Treatment options

Non–high-risk patients (WBC count ≤10 × 10⁹/L) The results of 2 recently reported pivotal phase 3 studies, comparing the efficacy and safety of ATRA plus ATO vs the standard ATRA plus chemotherapy, strongly support the former combination as the new standard of care for patients with non–high-risk APL.[5,6]

The first reported trial, conducted by the Italian cooperative group Gruppo Italiano Malattie Ematologiche dell' Adulto (GIMEMA) in collaboration with the German-Austrian AML Study Group (AMLSG) and Study Alliance Leukemia (SAL) cooperative groups, compared ATRA plus ATO with ATRA plus chemotherapy (AIDA regimen) in patients with low-to-intermediate risk APL (WBC count <10 × 10⁹/L). Patients were randomly assigned to receive either (a) ATRA plus ATO for induction (daily until complete remission [CR] or for a maximum of 60 days) and consolidation therapy (ATO 5 days per week, 4 weeks on 4 weeks off, for a total of 4 courses and ATRA 2 weeks on and 2 weeks off for a total of 7 courses) or (b) standard ATRA–idarubicin induction therapy followed by 3 cycles of consolidation therapy with ATRA plus chemotherapy and maintenance therapy with low-dose chemotherapy and ATRA. The results showed noninferiority and possible superiority of ATO plus ATRA without chemotherapy for both event-free and overall survival.[5] ATRA plus ATO was associated with significantly less myelosuppression and fewer infections, but more frequent increases in liver enzymes and QTc prolongation. These side effects, however, were reversible and manageable with temporary drug discontinuation and further dose adjustment in some cases. A recent update of this trial, analyzing an extended series of patients with a median follow-up of 41 months, showed that the event-free and overall survival advantages of ATRA plus ATO significantly increased over time, together with a statistically significant lower cumulative incidence of relapse rate in the ATO plus ATRA cohort, therefore also indicating greater efficacy of the latter regimen.[22]

Another randomized clinical trial, conducted by the National Cancer Research Institute (NCRI) cooperative group, compared ATRA plus chemotherapy with ATRA plus ATO in patients with APL regardless of WBC count.[6] The recently updated results[23] confirmed significantly higher event-free survival and lower cumulative incidence of relapse rates in patients receiving the ATO plus ATRA whereas overall survival was not statistically different in the 2 arms. The lack of difference in overall survival rates between the 2 arms might be explained by the recommended use of preemptive treatment with ATO for patients undergoing molecular relapse in the ATRA-plus-chemotherapy arm, which was enabled by high compliance with MRD monitoring. Despite the use of an attenuated schedule of ATO as frontline therapy, patients in the ATRA-plus-ATO arm not only had increased liver aspartate aminotransferase levels (although this was less frequent compared with the Italian-German trial), but also significantly less requirement for supportive care, compared with those treated with ATRA plus idarubicin. However, improvement in quality of life could not be demonstrated.

The long-term results of a nonrandomized study from a single institution[24] suggested that ATRA plus ATO results in sustained responses in patients with WBC counts ≤10 × 10⁹/L. Together with the results of the 2 above-mentioned phase 3 trials, these data strongly support the combination of ATRA and ATO without chemotherapy as the new standard of care for patients with non–high-risk APL. Nevertheless, in countries where chemotherapy is more affordable than ATO, the classical combination of ATRA and chemotherapy is still an acceptable option.

High-risk patients (WBC count >10 × 10⁹/L) Currently, there are 2 potential treatment options for high-risk patients, that is, ATRA plus ATO with the addition of some cytoreductive chemotherapy

and ATRA plus chemotherapy, because neither has yet been shown to be superior in randomized studies. Nevertheless, the use of ATO for high-risk patients may be problematic, at least in the United States and Europe because FDA and EMA approval is currently restricted to non–high-risk patients.

ATRA plus ATO–containing approaches The only randomized study that has been reported that compares ATRA plus chemotherapy vs ATRA plus ATO in high-risk APL patients did not show significant differences in outcomes.[6] In this study, high-risk patients in the ATRA-ATO arm also received a single dose of GO (6 mg/m^2).

Other ATRA plus ATO–based approaches, such as the regimen used by the MD Anderson Cancer Center[24] (using GO 9 mg/m^2 on day 1) and the Shanghai group,[25] including 3 courses of chemotherapy as consolidation, also reported outstanding long-term results in the non–high-risk group, whereas outcomes for the high-risk group reported in these studies did not significantly improve those reported with ATRA and chemotherapy.[26-28]

Another interesting ATRA plus ATO–based regimen was used by the Australasian Leukaemia and Lymphoma Group (ALLG). Compared with a historical ATRA-chemotherapy control and despite a 50% reduction in idarubicin exposure, this study confirmed outstanding outcomes, not only in low- but also in high-risk patients, with no significant differences between both risk categories.[10] These results have led to the approval of ATO for APL patients of all risk groups in Australia. The protocol consisted of an induction with ATRA, ATO, and 4 doses of idarubicin (6-12 mg/m^2, adjusted for age), followed by 2 consolidation courses of ATRA and ATO, and then by 2 years of maintenance therapy with ATRA and low-dose chemotherapy.[29] These promising results reported in a small series of high-risk patients need to be confirmed in larger series.

It should be emphasized that the heterogeneity of single-arm studies with ATO plus ATRA combining different schedules of chemotherapy does not allow for recommendation of a specific regimen for high-risk APL (apart from the control of high WBC count). Furthermore, eligible patients should therefore receive conventional treatment or be treated within prospective clinical trials (eg, APOLLO, NCT02688140).

ATRA plus chemotherapy Studies combining ATRA and chemotherapy reported over the last 2 decades have shown a virtual absence of primary resistance, 90% to 95% CR rates, and 85% to 90% rates of long-term survival. Best results with ATRA plus chemotherapy are obtained with simultaneous administration of ATRA and anthracycline-containing chemotherapy for induction. Comparable CR rates have been reported using either ATRA plus daunorubicin and cytarabine or ATRA plus idarubicin alone, with no apparent advantage observed by adding other cytotoxic agents. Consolidation therapy should entail administration of at least 2, and possibly 3, further cycles of ATRA plus anthracycline–containing chemotherapy. Some recent studies have reported molecular persistence rates <1% after consolidation when ATRA was given for 15 days in conjunction with 3 courses of anthracycline-based risk-adapted chemotherapy.[26,27] A recent comparison of the Programa Español de Tratamientos en Hematología (PETHEMA)/Hemato-Oncologie voor Volwassenen Nederland (HOVON) and the International Consortium on APL regimens using idarubicin[26] and daunorubicin,[30] respectively, indicated that the 2 drugs were associated with similar rates of primary resistance, molecular persistence of disease, and molecular and hematological relapse rates.[31] Although the addition of intermediate- or high-dose cytarabine during consolidation has been questioned,[32] the majority of studies suggest a potential benefit in terms of reduction of relapse risk for the addition of at least 1 cycle of intermediate- or high-dose cytarabine in patients younger than 60 years of age with WBC counts higher than 10 × 10^9/L.[26,27,33] However, chemotherapy intensification is associated with some deaths in CR and no differences were reported in overall survival.

A large randomized trial involving most European cooperative groups (APOLLO study, NCT02688140) to compare ATRA plus ATO and the addition of 2 doses of idarubicin for induction vs ATRA and chemotherapy has been recently initiated for high-risk APL patients.

Considerations on dosing, schedules, and formulations of ATO The therapeutic advantage obtained with ATRA and ATO compared with ATRA and chemotherapy in non–high-risk patients has been achieved with 2 different ATO dosing schedules. Although the Italian-German trial[5] used a more frequent dosing schedule of ATO (up to 140 doses of 0.15 mg/kg), the NCRI trial[6] used a less frequent dosing schedule (63 doses of 0.25-0.30 mg/kg). The intensity of ATO in the 2 schedules is, however, almost identical with respect to total ATO dose in milligrams per kilogram: the main difference being related to the scheduling and duration of treatment. Indeed, ATO was given at lower doses on a daily basis in the Italian-German trial whereas the NCRI study used the higher dose administered 2 or 3 days per week. Regarding the duration of ATO during induction therapy, in the NCRI trial, the drug was given at a dose of 0.3 mg/kg on days 1 to 5 in week 1 followed by 0.25 mg/kg twice weekly for 7 weeks, whereas in the Italian-German trial, the drug was given at a dose of 0.15 mg/kg daily until CR.

Uncertainty remains regarding how to counteract hyperleukocytosis occurring during induction with ATRA and ATO. Approximately 70% of non–high-risk patients treated with ATO develop leukocytosis with induction, with a median peak WBC count of 20 × 10^9/L at ~10 days from the start of treatment.[24] With marked hyperleukocytosis (over 10 × 10^9/L) developing during ATO, administration of hydroxyurea (2 g per day) or 1 to 2 doses of idarubicin (12 mg/m^2) or gemtuzumab ozogamicin (6-9 mg/m^2) can be considered, although their clinical benefit is unclear.

Several recent studies, conducted in either newly diagnosed or relapsed patients, have shown that oral arsenic derivatives may be a valid alternative to IV ATO.[34-36]

The Chinese APL Cooperative Group[35] has recently reported 2 randomized noninferiority studies comparing IV ATO vs an oral tetrasulfide arsenic formulation (Realgar–indigo naturalis formula [RIF]) in newly diagnosed APL. The first study used ATRA and arsenic derivatives for both induction and maintenance therapy, as well as chemotherapy for consolidation in both arms,[35] whereas the most recent one compared 2 completely chemotherapy-free schedules in non–high-risk patients.[37] Both trials demonstrated that oral RIF plus ATRA was not inferior to IV ATO plus ATRA as

first-line treatment. RIF has been commercialized and is commonly available in China, whereas it is not licensed elsewhere.

A single-center study from Hong Kong using an oral formulation of ATO has also provided excellent long-term outcomes in relapsed APL.[36] In Australia, a capsule-based oral formulation of ATO is currently undergoing bioavailability testing by the ALLG (ACTRN12616001022459), and an upcoming international multicenter phase 3 trial comparing ATRA plus oral ATO vs ATRA plus IV ATO in patients with non–high-risk APL will be conducted in the United States and Europe with the aim of establishing the role of oral arsenic derivatives in frontline therapy.

Central nervous system prophylaxis

We refer to the recommendations for central nervous system (CNS) prophylaxis published in the 2009 report.[4] Although there are no formal data supporting the use of CNS prophylaxis in the ATO era, if CNS prophylaxis is used, its use should be restricted to patients with WBC counts $>10 \times 10^9$/L at presentation, or to those who have had a CNS hemorrhage for whom the risk of CNS relapse increases substantially.[38]

It is strongly advisable to postpone any CNS prophylaxis until after the achievement of CR because lumbar puncture at presentation and during induction can be extremely hazardous.

Response criteria and outcome measures after induction

Because disease resistance has practically disappeared, CR is currently attained in virtually all patients with genetically proven PML/RARA APL given standard ATRA plus chemotherapy or ATRA plus ATO who do not die due to complications. This fact should be considered because the morphological pattern in the BM when using ATO and ATRA may differ considerably from that observed using conventional AML cytotoxic therapy. Potentially misleading cytomorphologic features due to incomplete blast differentiation are commonly seen in APL during the first 3 to 4 weeks of induction therapy and occasionally up to 40 to 50 days. This delayed differentiation of blasts can lead to the detection of cells displaying t(15;17) by conventional cytogenetics or FISH, particularly when these tests are performed immediately after induction. The same applies to early molecular evaluation carried out soon after induction. In a randomized study,[11] RQ-PCR analysis for PML-RARA after induction therapy showed that the proportion of patients with detectable transcripts at the postinduction time point was higher in the ATRA-ATO arm than in the ATRA-chemotherapy arm (76% and 63%, respectively), obviously reflecting delayed maturation and slow clearance of leukemic cells rather than resistance. These morphologic, cytogenetic, and molecular findings are not indicative of therapy failure and do not justify any treatment modification. It is important that treatment with differentiating agents (ATRA or ATO) be continued until terminal differentiation with <5% of blasts in the BM. The reported median time to CR using ATRA plus ATO or chemotherapy is 4 to 5 weeks, however, a proportion of patients requires continuation of ATO and/or ATRA for up to 8 to 10 weeks.

Keeping in mind the virtual absence of disease resistance and the frequently misleading persistence of late maturing blasts at postinduction morphologic assessment, as well as a lack of important prognostic factors at this time point, the indication for BM assessment after induction is questionable, except for research purposes.

Response criteria and outcome measures at the end of consolidation and beyond

In sharp contrast to the lack of clinical value of molecular assessment performed at the end of induction, molecular analysis of BM collected after the completion of consolidation is crucial to determine relapse risk.[39,40] The achievement of molecular remission at the end of consolidation corresponds to the new ELN AML response category "CR without minimal residual disease (CR_{MRD-})."[41] which is thus a major treatment objective in both APL and AML.

Given the impact of MRD positivity detected at the end of consolidation on decision-making, the panel still recommends performing a confirmatory test to collect a new marrow sample within 2 weeks using a reference laboratory for independent confirmation. Repeat testing is recommended in cases of conversion from MRD^- to MRD^+ during follow-up prior to institution of salvage therapy.

Because early treatment intervention in patients with evidence of MRD affords a better outcome than treatment in full-blown relapse, MRD monitoring of BM has been used in routine clinical practice for all patients. However, the striking outcome improvements obtained with modern treatments call into question the benefit of stringent and prolonged monitoring of MRD, at least in non–high-risk patients (WBC count $\leq 10 \times 10^9$/L) where the risk of relapse is extremely low. Given uncertain cost-effectiveness, postconsolidation MRD monitoring can be avoided in this setting and performed only in high-risk patients (WBC count $>10 \times 10^9$/L) in routine clinical practice. This is in contrast to recently reported recommendations from the ELN MRD Working Party.[42] Although the NCRI group suggested that longitudinal monitoring postconsolidation at the 3-month interval could be carried out in patients receiving ATRA and chemotherapy, with the intent to administer ATO-based salvage early at the time of molecular relapse,[43] we reiterate that MRD monitoring can be avoided in non–high-risk patients who achieve CR_{MRD-} status after consolidation, not only in patients treated with ATRA plus ATO, but also in those with ATRA plus chemotherapy. We also do not recommend MRD evaluation after induction outside of clinical trials, and emphasize again that MRD evaluation postinduction should definitely not influence therapeutic decisions.

RQ-PCR is currently the standard method for molecular monitoring in APL. As compared with qualitative RT-PCR tests, RQ-PCR is less prone to contamination, allows for a better assessment of disease response kinetics, and enables better identification of poor-quality samples that could result in "false-negatives."[40] A longitudinal comparative RQ-PCR study of paired BM and PB samples for PML/RARA monitoring showed an earlier detection of molecular relapse in BM.[43] These data suggest that BM sampling remains the preferred approach. Nevertheless, monitoring in PB remains a reasonable, pragmatic, and more comfortable option for the patient. Allowing more frequent monitoring of blood than would be possible for marrow would make the sensitivity for detection of relapse similar between the 2 options.[42]

MRD positivity clearly exists when RT-PCR is positive using low sensitive methods (threshold detection roughly 1 cell in 10^4) at 2 consecutive time points at least ~4 weeks apart. With RQ-PCR

Table 2. Management during induction, consolidation therapy, and beyond

Recommendation	Level of evidence–grade of recommendation	Changes compared with the 2009 recommendations
2.1. Eligible patients should be offered entry into a clinical trial	IV–C	Unchanged
Induction therapy		
2.2. For patients with a WBC count ≤10 × 10^9/L, induction therapy should consist of ATRA and ATO without chemotherapy; ATRA and anthracycline–based chemotherapy is a second option when ATO is contraindicated or unaffordable	Ib–A	New recommendation
2.3. For patients with a WBC count >10 × 10^9/L, there are 2 valid options, either ATRA + ATO with a certain amount of chemotherapy or conventional ATRA + anthracycline–based chemotherapy	Ib–A	New recommendation
2.4. Induction therapy should not be modified based on the presence of leukemia cell characteristics that have variably been considered to predict a poorer prognosis (eg, secondary chromosomal abnormalities, FLT3 mutations, CD56 expression, and BCR3 *PML-RARA* isoform)	IIa–B	Unchanged
2.5. Treatment with ATRA should be continued until terminal differentiation of blasts and achievement of CR, which occurs in virtually all patients following conventional ATRA + anthracycline or ATRA + ATO induction treatment	IIa–B	Updated
2.6. Clinicians should refrain from making therapeutic modifications on the basis of incomplete blast maturation (differentiation) detected up to 50 d or more after the start of treatment by morphology or cytogenetic or molecular assessment	IV–C	Unchanged
Consolidation therapy		
2.7. For patients treated with chemotherapy-free approaches, 4 consolidation courses of ATO (0.15 mg/kg/d 5 days/wk, 4 wk on 4 wk off) and 7 courses of ATRA (45 mg/m^2/d for adults; 25 mg/m^2/d for children, 2 wk on 2 wk off) are recommended	Ib–A	New recommendation
2.8. For patients treated with the conventional ATRA + chemotherapy approach:		Slightly modified
• 2-3 courses of anthracycline-based chemotherapy should be given for consolidation therapy	Ib–A	
• The addition of ATRA to chemotherapy in consolidation seems to provide a clinical benefit	IIb–B	
• Consolidation for high-risk patients younger than 60 years of age with WBC counts higher than 10 × 10^9/L should include at least 1 cycle of intermediate- or high-dose cytarabine	IIb–B	
2.9. Molecular remission in the BM should be assessed at completion of consolidation by RT-PCR or RQ-PCR assay affording a sensitivity of at least 1 in 10^4	IIa–B	Slightly modified
Management after consolidation		
2.10. For patients treated with chemotherapy-free approaches (WBC count ≤10 × 10^9/L), no maintenance is needed	Ib–A	New recommendation
2.11. For patients treated with conventional ATRA + chemotherapy approaches: maintenance therapy should be used for patients who have received an induction and consolidation treatment regimen wherein maintenance has shown a clinical benefit	Ib–A	Unchanged
2.12. Because early treatment intervention in patients with evidence of MRD affords a better outcome than treatment in hematologic relapse, MRD monitoring of BM every 3 mo should be offered to high-risk patients (WBC count >10 × 10^9/L) for up to 3 y after completion of consolidation therapy; given the very low probability of relapse for non–high-risk patients (WBC count ≤10 × 10^9/L), prolonged MRD monitoring could be avoided in this setting or carried out using PB	IIb–B	Slightly modified
2.13. BM generally affords greater sensitivity for detection of MRD than blood and therefore is the sample type of choice for MRD monitoring to guide therapy	IIa–B	Unchanged
2.14. For patients testing PCR^+ at any stage following completion of consolidation, it is recommended that a BM is repeated for MRD assessment within 2 wk and that samples are sent to the local laboratory, as well as to a reference laboratory for independent confirmation	IV–C	Unchanged
2.15. CNS prophylaxis can be considered only for patients with hyperleukocytosis	IV–C	Unchanged

Table 3. Management of special situations

Recommendation	Level of evidence–grade of recommendation	Changes compared with the 2009 recommendations
Older patients		
3.1. Elderly patients in good clinical condition treated with chemotherapy-based regimens should be managed with a treatment approach similar to that used in younger patients, but slightly attenuated in dose intensity; although the experience with chemotherapy-free approaches in this setting is very limited, it seems reasonable to follow a similar strategy for patients with non–high-risk APL	IIa–B	Slightly modified
Patients with severe comorbidities		
3.2. Older and younger patients with severe comorbidities unfit for chemotherapy (especially anthracyclines) are candidates to receive ATO-based treatment schedules	III–B	Unchanged
Children		
3.3. ATRA at 25 mg/m^2/d is the recommended dose in children and adolescents	IIa–B	Unchanged
Pregnant women		
3.4. Management of APL in pregnancy requires the involvement of the patient, hematologist, obstetrician, and neonatologist	III–B	Unchanged
3.5. Retinoids are highly teratogenic and should be avoided in the first trimester unless the patient decides to have a termination of pregnancy	III–B	Unchanged
3.6. ATRA can be used in the second and third trimesters of pregnancy	III–B	Unchanged
3.7. Arsenic derivatives are highly embryotoxic and are contraindicated at any stage of pregnancy	IV–C	Unchanged
3.8. In patients presenting in the first trimester and not wishing to have a termination of pregnancy, induction therapy with daunorubicin alone can be offered	IV–C	Unchanged
3.9. Although chemotherapy appears reasonably safe in the second and third trimester of pregnancy, it is associated with an increased risk of abortions and premature delivery, and induction of labor between cycles of chemotherapy should be considered	III–B	Unchanged
3.10. Stringent fetal monitoring, with particular emphasis on cardiac function, is recommended for patients receiving ATRA with or without chemotherapy during pregnancy	IV–C	Unchanged
3.11. For deliveries before 36 wk of gestation, antenatal corticosteroids before preterm delivery are recommended to reduce the risk of fetal morbidity and mortality associated with respiratory distress syndrome	IIb–B	Unchanged
3.12. After successful delivery, breastfeeding is contraindicated if chemotherapy or ATO is needed	IV–C	Unchanged
3.13. Female patients with APL should be advised against conceiving while exposed to ATRA or ATO for consolidation and maintenance therapy	IV–C	Unchanged
Management of therapy-related APL		Unchanged
3.14. Patients with tAPL should be treated like those with de novo APL, but modifications may be necessary taking into account cardiac toxicity and prior anthracycline exposure	III–B	Unchanged

tAPL, therapy-related APL.

methods, which typically are marginally more sensitive than RT-PCR (median, $10^{4.2}$; range, $10^{2.9}$-$10^{5.2}$),[43,44] interpretation can be difficult when the transcript number is low in the context of a high-sensitivity assay ($\geq 10^5$). In these cases, the most reliable indicator of true MRD positivity is the observation of increasing copy number of PML/RARA transcripts in at least 2 successive BM samples.

With regard to giving precise recommendations for long-term follow-up intervals of patients who have achieved an MRD$^-$ status, there are no data. However, it seems reasonable to perform blood counts once a month during the first 12 months after diagnosis, and at 3- to 4-month intervals during the first 2 to 3 years.

Management after consolidation

The rare cases with molecular persistence of disease at the end of consolidation, and the more common molecular relapse, are highly predictive of early hematological (morphologic) relapse.[45,46] Therefore, patients with molecular persistence or molecular relapse require immediate additional treatment, including transplantation (hematopoietic stem cell transplantation [HSCT]) if feasible. In patients showing molecular persistence or molecular relapse after ATRA plus chemotherapy, ATRA plus ATO can be used to achieve a new molecular remission.[43] ATRA plus chemotherapy remains an option when molecular persistence occurs after frontline therapy with ATRA plus ATO.

Table 4. Sensitivity to ATRA and ATO of the 12 fusion genes involving RARA that have been recognized so far, excluding PML-RARA

RARA rearrangements	Translocations	No. of cases reported	ATRA sensitivity	ATO sensitivity	First report Ref.
ZBTB16-RARA	t(11;17)(q23;q21)	>30	Poorly responsive	Poorly responsive	64
NPM-RARA	t(5;17)(q35;q21)	?	Sensitive	ND	65
NuMA-RARA	t(11;17)(q13;q21)	1	Sensitive	ND	66
STAT5b-RARA	der(17)	9	Poorly responsive	Poorly responsive	67
PRKAR1A-RARA	t(17;17)(q21;q24) or del(17)(q21;q24)	1	Sensitive	Sensitive	68
FIP1L1-RARA	t(4;17)(q12;q21)	2	Sensitive in 1 case	ND	69
BCoR-RARA	t(X;17)(p11;q21)	2	Sensitive in 2 cases	Insensitive in 1 case	49
OBFC2A-RARA	t(2;17)(q32;q21)	1	Sensitive, in vitro sensitive in 1 of 2 cases	ND	50
TBLR1-RARA	t(3;17)(q26;q21)	1	Insensitive	ND	51
GTF2I-RARA	t(7;17)(q11;q21)	1	Sensitive	Sensitive	52
IRF2BP2-RARA	t(1;17)(q42;q21)	3	Sensitive	Sensitive	53
FNDC3B-RARA	t(1;17)(q42;q21)	1	Sensitive	Sensitive	54

ND, not determined; Ref., reference citation number.

The use of GO may also be considered in both situations, but always as a bridge to HSCT, although it may confer a risk of veno-occlusive disease/sinusoidal obstructive syndrome. Optimal therapy in patients unsuitable for HSCT is not well established.

The role of maintenance therapy in patients treated with ATRA and chemotherapy–based approaches remains controversial, particularly in non–high-risk patients. However, the outstanding results reported using ATRA plus ATO approaches without maintenance therapy suggest that this phase of treatment has no role in this setting.[5,6] As for high-risk patients, maintenance therapy may still play a role for those receiving ATRA and chemotherapy while its omission in the setting of ATRA and ATO is currently under investigation. A recent randomized study of the Japanese Adult Leukemia Study Group has demonstrated a significant benefit in relapse-free survival of tamibarotene over ATRA in maintenance therapy, especially in high-risk patients who obtained molecular remission with ATRA and chemotherapy.[47]

Given the extreme rarity of relapse in low-risk patients who are PCR^{-} after completion of consolidation, the panel concluded that there was no need for blood or marrow PCR monitoring after this time in these patients.

Recommendations on management during induction, consolidation therapy, and beyond are listed in Table 2.

Management of special situations and APL molecular variants

Previous ELN recommendations[4] have not been modified, except for patients with severe comorbidities or older patients (Table 3).

Two randomized trials have shown the efficacy and safety of ATO-plus-ATRA approaches in older patients.[5,6] Based on the results of recent trials, it seems reasonable to extend this approach to patients with comorbidities or those who are very elderly who are deemed unfit for chemotherapy but considered fit for ATO. Similarly, the chemotherapy-free regimen is being investigated in children with newly diagnosed APL by the Children's Oncology Group[48] (NCT02339740) and other cooperative groups worldwide. The use of ATO in the treatment of children with APL may not only reduce exposure to a high cumulative dose of anthracycline and, therefore, reduce some of the long-term side effects, but also may increase efficacy in a patient population with higher prevalence of high-risk disease.

The 2009 ELN recommendations for management of APL in pregnancy are unchanged.

In addition to the 6 extremely rare RARA fusion variants recognized before 2009 (ZBTB16-RARA, NPM-RARA, NuMA-RARA, STAT5b-RARA, PRKAR1A-RARA, and FIP1L1-RARA),[4] 6 new RARA partner genes have been described in recent years: BCoR,[49] OBFC2A,[50] TBLR1,[51] GTF2I,[52] IRF2BP2,[53] and FNDC3B.[54] Table 4 shows the limited information available on the sensitivity to ATRA and ATO of the 12 genetic variants involving RARA currently recognized, excluding *PML-RARA*. The appropriate management of patients with these RARA fusion products is still unknown because other than for ZBTB16/RARA, the evidence mostly consists of single case reports. As a general rule, treatment of patients with ATRA-sensitive variants should include this agent in combination with anthracycline-based chemotherapy, whereas in those with ATRA-resistant variants,

Table 5. Management of molecular persistence, molecular relapse, and hematologic relapse

Recommendation	Level of evidence–grade of recommendation	Changes compared with the 2009 recommendations
5.1. For patients with confirmed molecular relapse (defined as 2 successive PCR$^+$ assays, with stable or rising *PML-RARA* transcript levels detected in independent samples analyzed in 2 laboratories), preemptive therapy has to be started promptly to prevent frank relapse	IIa–B	Unchanged
5.2. Salvage therapy for molecular persistence after consolidation, molecular relapse, or hematologic relapse should be chosen considering the previously used first-line treatment and duration of first relapse: • Patients relapsing after ATRA + chemotherapy should be managed with ATRA + ATO–based approaches • Patients relapsing after ATRA + ATO should be managed with ATRA + chemotherapy • A potential exception for crossing over to a different treatment of relapsed patients may be considered for those with late relapse (eg, CR1 >2 y)	IV–C	New recommendation
5.3. Patients achieving second CR should receive intensification with HSCT or chemotherapy, if possible	IV–C	Unchanged
5.4. Allogeneic HSCT is recommended for patients failing to achieve a second molecular remission	IV–C	Unchanged
5.5. Autologous HSCT is the first option for patients without detectable MRD in the marrow and with an adequate PCR$^-$ harvest	IIa–B	Slightly modified
5.6. For patients in whom HSCT is not feasible, the available options include repeated cycles of ATO with or without ATRA with or without chemotherapy	IV–C	Unchanged
5.7. For patients with CNS relapse, induction treatment consists of weekly triple ITT with methotrexate, hydrocortisone, and cytarabine until complete clearance of blasts in the cerebrospinal fluid, followed by 6-10 more spaced out ITT treatments as consolidation; systemic treatment should also be given following recommendations 5.1 to 5.6	IV–C	Unchanged

CR1, first CR; ITT, intrathecal therapy.

the addition of ATRA is less attractive and management should consist of AML-like approaches.

Management of molecular and hematologic relapse

Previous ELN recommendations for the management of relapse were entirely focused on patients who relapsed following ATRA plus chemotherapy as first-line treatment.[4] Here, 2 independent retrospective studies reported that early treatment intervention in patients with molecular relapse affords a better outcome than treatment only at hematologic relapse.[55,56] Hence the recommendation (unchanged since 2009) is to promptly start preemptive therapy in order to prevent hematologic relapse. Salvage therapy for molecular or hematologic relapse should be chosen considering the previously used first-line treatment (Table 5). Thus, patients who relapsed after ATRA plus chemotherapy should be treated with an ATRA plus ATO–based approach as salvage therapy until achievement of MRD negativity, whereas for those relapsing after ATRA plus ATO, an ATRA-plus-chemotherapy approach could be the most appropriate option. A potential exception for crossing over to a different treatment for patients who relapsed may be considered for those with late relapse (eg, >2 years in CR).

Regardless of scenario, the main objective of salvage therapy is the achievement of molecular remission as a bridge to HSCT. Based on recent studies,[57-62] autologous HSCT should be considered the first choice for eligible patients achieving second molecular remission. However, a recent NCRI report questions the role of transplantation, at least in patients achieving molecular remission with ATO and ATRA who do not have CNS disease at relapse and who have received a full course of consolidation with ATO.[23] Patients failing to achieve molecular remission are candidates for allogeneic HSCT. Patients unsuitable for HSCT and those with a very prolonged CR1 can be managed with some type of continuation therapy chosen considering previous treatments and clinical condition.

A recently reported association between PML mutations occurring in the hotspot domain (C212-S220) and arsenic-resistant disease, if confirmed, may be helpful in guiding treatment choices.[63]

Recommendations regarding CNS and other extramedullary relapses remain the same.

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Authorship

Contribution: M.A.S., E.H.E., and F.L.-C. drafted the manuscript and integrated all changes and suggestions made by the rest of authors, who also reviewed the manuscript and contributed to the final draft.

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Footnote

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Appendix

These classifications are used in Tables 1-3 and 5.

Levels of evidence

Level	Type of evidence
Ia	Evidence obtained from meta-analysis of randomized controlled trials
Ib	Evidence obtained from at least 1 randomized controlled trial
IIa	Evidence obtained from at least 1 well-designed controlled study without randomization
IIb	Evidence obtained from at least 1 other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed nonexperimental descriptive studies, such as comparative studies, correlation studies, and case control studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Grading of recommendations

Grade	Recommendation
A (Evidence-level quality Ia, Ib)	Requires at least 1 randomized controlled trial as part of the body of literature of overall good, and consistency addressing the specific recommendation
B (Evidence levels IIa, IIb, III)	Requires availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation
C (Evidence level IV)	Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities; indicates absence of directly applicable studies of good quality

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