Belgium recommendations for the management of acute promyelocytic leukaemia

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The management of acute promyelocytic leukaemia has evolved considerably. The standard front-line approach with all-trans retinoic acid and chemotherapy has recently been challenged by the chemo-free combination of all-trans retinoic acid and arsenic trioxide, which has emerged as the new standard of care for non-high-risk disease. This review gives an update of the management of acute promyelocytic leukaemia.
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Introduction

Acute promyelocytic leukaemia (APL) is a particular subtype of acute myeloid leukaemia (AML) characterised by the distinct morphology of the blast cells, a potentially life-threatening coagulopathy and a specific balanced translocation, t(15;17), resulting in the fusion of promyelocytic leukaemia (PML) and retinoic acid receptor-α (RARα) genes.[1]

APL is a rare disease with an incidence rate of 0.14 APL cases per 100 000 each year in Europe. In Belgium, the national cancer registry has published 105 cases for the period 2009-2013, leading to an approximate incidence rate of 0.19 cases per 100 000 per year.[2,3]

Clinical presentation

Patients often present with peripheral cytopenias, including a low or normal total white blood cell count (WBC) in 75% of the cases. APL often presents with coagulative abnormalities, including disseminated intravascular coagulation (DIC), hyperfibrinolysis and unspecific proteolysis leading to severe bleeding complications, in particular at initial presentation and in the first treatment phase.[1]

Diagnosis

Initial diagnostic work-up is based on morphology (hypergranular blast cells with Auer rods, Faggot-cells) and immunophenotyping, typically revealing strong positivity for CD33, expression of CD117 and CD13, infrequent expression of HLA-DR and CD34, and absence of CD11a, CD11b and CD14 on the surface of APL blasts. The final confirmation of diagnosis should be carried out by cytogenetics [t (15;17)(q22;q11-12)] and molecular biology.[1,4]

Detection of PML-RARα fusion is carried out by fluorescence in situ hybridisation (FISH) and/or by real time-polymerase chain reaction (RT-PCR). RT-PCR is a highly sensitive technique used not only to confirm the presence of the PML/RARα fusion gene at diagnosis but also to track minimal residual disease (MRD) during and after treatment. Alternative fusion partners are the zinc finger (PLZF), the nucleophosmin gene (NPM), the nuclear mitotic apparatus (NUMA) or the STAT5b gene. These fusion partners may be of therapeutic relevance (e.g. resistance to all-trans retinoic acid (ATRA), with the involvement of the PZLF gene).[4]

Prognostic risk factors

Besides age, the most important prognostic factor in APL is the initial leukocyte count enabling to stratify patients into a high-risk group (>10000 leucocytes/mcl) and a good-risk group (<10000 leucocytes/mcl).[5,6]

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Table 1. Recommendation for the initial phase management of APL adapted from Cicconi and Lo-Coco.[1]

Therapeutic intervention	Recommendation
Initiation of therapy ATRA and Chemotherapy or ATRA and/or ATO	Upon clinical and/or morphological suspicion of APL, ATRA and/or ATO should be started **immediately** (without waiting genetic confirmation of diagnosis).
Supportive care	**Aggressive supportive** care should be initiated **immediately** upon clinical and/or morphological suspicion of APL: • Strict monitoring of blood-count and coagulation parameters (every 6h) • Platelet-transfusion: maintain Plts > $50x10^9$/L • Plasma-transfusion: maintain fibrinogen > 1,5 g/l • Avoid anticoagulation (e.g.: Heparin)
Confirmation of diagnosis	**Genetic confirmation** is mandatory: Fish and/or RT-PCR are preferred. RT-PCR delivers further information for MRD-monitoring during treatment.
Prophylaxis of Differentiation Syndrome	**Steroids** are generally recommended, particularly in patients with elevated WBC counts (>$5x10^9$/L). The type of steroid and the duration is matter of debate. e.g.: Dexamethasone 10 mg/12h
To be avoided	**Invasive procedures** (risk of bleeding and/or thrombosis) until resolution of coagulation disorders (e.g. lumbar puncture, placement of CVC or arterial lines, leukapheresis, etc).

ATRA: All-trans retinoic acid; ATO: arsenic trioxide; RT-PCR: real time polymerase chain reaction; Ara-C: Cytarabine; Plts: Platelets.

Treatment

Treatment of APL has greatly evolved over the last 60 years. However, APL treatment is still challenging, in particular during induction therapy. High rates of cure can only be achieved in highly specialised centres with well trained staff and standardised procedures, including aggressive supportive care (*Table 1*).[1,4] Several drugs are used in APL treatment, mostly in combination: anthracyclines, cytarabine (Ara-C), ATRA, and arsenic trioxide (ATO).[1,6]

ATRA/Chemo-based therapy

Until recently, the recommended treatment of APL was based on concomitant application of chemotherapy – mainly anthracyclines – and ATRA. In comparison to conventional chemotherapy this combination has shown consistently higher complete response (CR) rates (>95%) as well as prolonged remission duration in either randomised or historical comparisons. The most widely used combination for induction therapy, irrespective of APL risk, is the combination of ATRA plus idarubicin (AIDA).[1,6]

As it has been demonstrated that molecular remission can be achieved in more than 90% of patients if at least two cycles of an anthracycline-containing consolidation are used, this is considered the present therapeutic standard for all patients with APL in CR after induction chemotherapy. Even though there is no comparative study on the efficacy of ATRA in addition to chemotherapy during consolidation, historical comparisons have demonstrated that incorporation of ATRA contributes to improved outcome.[1,6]

The role of Ara-C in APL has long been controversial. However, comparative cohort studies in high-risk patients (WBC >10000 leucocytes/mcl) show positive effects with significantly higher remission rates, better disease-free and overall survival, and thus favouring the addition of Ara-C during consolidation for high-risk patients.[6,7]

Maintenance therapy

Despite controversial results, maintenance therapy is still included in most ATRA-plus-chemotherapy-based protocols. Due to the high cure rate with ATRA and chemotherapy in APL, there is no indication for hematopoietic stem cell transplantation (HSCT) in patients who are in first molecular remission after completion of consolidation therapy.[1,6,8]

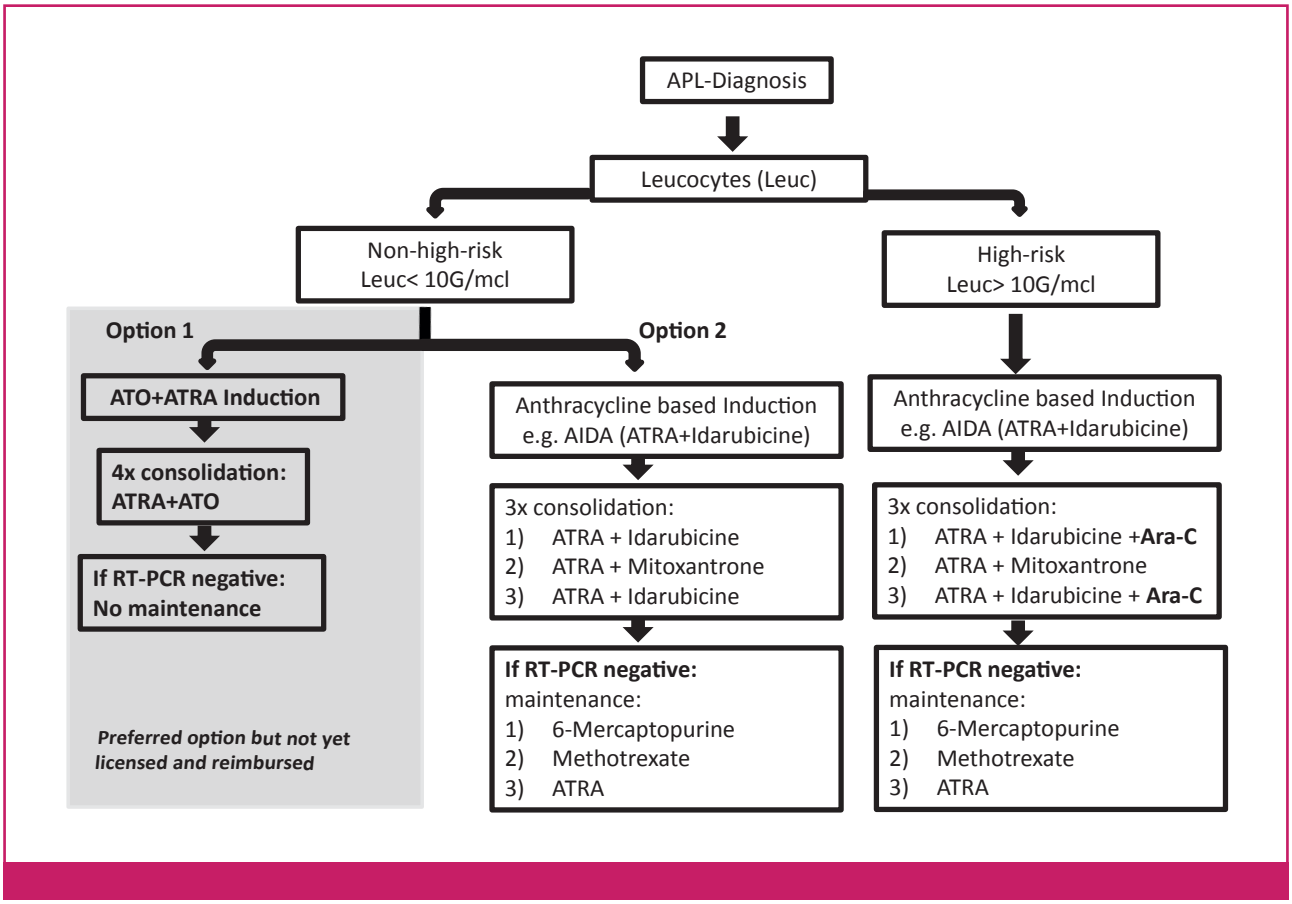

Figure 1. Treatment guidelines for newly diagnosed APL adapted from German intergroup recommendations on the diagnostic and therapeutic management of acute promyelocytic leukemia.[4]

Age: even above 70 should not be an obstacle to treat; ATRA: All-trans retinoic acid; ATO: arsenic trioxide; RT-PCR: real time polymerase chain reaction; Ara-C: Cytarabine.

Arsenic trioxide in APL

ATO is the most effective single agent in APL. ATO is actually licensed for the treatment of relapsed and refractory APL in the USA and Europe and has been shown to induce remission rates in up to 90% of these patients.[6] ATO is usually well tolerated. Adverse events such as hyperleukocytosis, increase of liver enzymes, APL differentiation syndrome, and prolongation of the QT interval are manageable.[4] The anti-leukemic efficiency of ATO is increased when combined with ATRA. Results of various studies conducted with ATO as single agent or combined with ATRA for newly diagnosed APL patients reported CR rates of 86-95%, molecular remission rates after two cycles of 76-100% and survival rates of 86-88%, with significantly better responses being obtained in patients with non-high-risk disease as compared to high-risk patients.[1,4]

Recently, two important randomised clinical studies, the APL0406 Intergroup Study (GIMEMA-AML-SG/SAL) and the British UK NCRI AML17 trial, investigated the use of the chemo-free combination ATO plus ATRA as first-line treatment in APL compared to a 'conventional' anthracycline based therapy (AIDA). Both trials show that ATO plus ATRA is at least as effective as the 'conventional' treatment arm in non-high-risk APL patients.[9,10] In particular, early mortality was almost absent in the treatment arm combining ATO and ATRA. Further results favouring the use of ATO in the first-line treatment come from the North American Intergroup evaluating ATO in first-line therapy during consolidation, demonstrating that ATO reduced the risk of relapse and improved survival.[11]

Based on these recent results, the recommendations of first-line treatment of APL have to be revised and the chemo-free ATO plus ATRA combination should be strongly considered for induction of non-high-risk patients (WBC <10 Gpt/l). Unfortunately this combination is not yet licensed for the first-line treatment of APL and clinicians should be aware of reimbursement problems. Treatment recommendations of the German

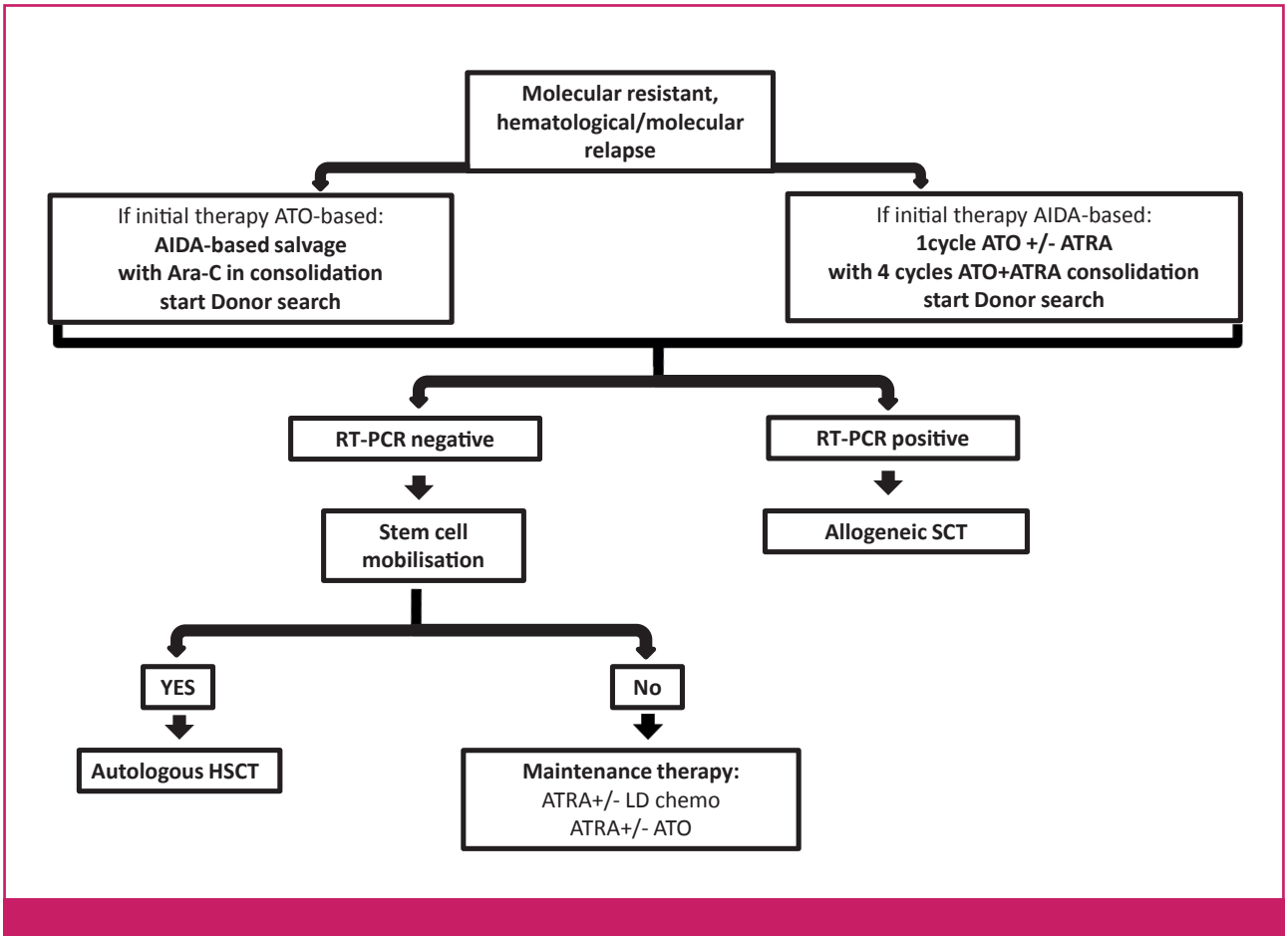

Figure 2. Salvage-strategy depending on first-line treatment adapted from German intergroup recommendations on the diagnostic and therapeutic management of acute promyelocytic leukemia.[4]

ATRA: All-trans retinoic acid; ATO: arsenic trioxide; RT-PCR: real time polymerase chain reaction; Ara-C: Cytarabine.

Intergroup (SAL/AML-CG/AML-SG), published in 2015, are depicted in adapted form in *Figure 1*.[4] There is less data concerning the treatment of elderly patients (with ATRA and chemotherapy or ATRA in combination with ATO) but available reports encourage an ATRA-based treatment even in patients above 70 years.[12] The European LeukemiaNet recommendations favour treatment without upper age limit.[6,13] In this context, considering the high curative potential and the excellent tolerance of ATO, older or unfit patients are probably a particular target group for the chemotherapy-free approach using ATO and ATRA.[14]

Treatment of minimal residual disease or relapse

In case of persistence of minimal residual disease (MRD) with PML/RARA detection, molecular or haematological relapse, the treatment of choice is ATO plus ATRA for induction and consolidation.[6] In case of relapse after ATO use in first-line treatment, a 'conventional' anthracycline based schedule (e.g. AIDA) should be used.[4] This should be followed by further post consolidation therapy. Autologous HSCT after high-dose therapy contributes to the stabilisation of remission, provided that PML/RARα is negative by PCR in the autologous graft and in the patient bone marrow prior to transplantation. In patients not achieving clearance of MRD by conventional therapy including ATO, an allogeneic HSCT should be considered (*Figure 2*).[4]

Conclusion

Acute promyelocytic leukaemia is a medical emergency. Appropriate diagnosis and immediate start of treatment can reduce the risk of early mortality. The chemo-free approach with the combination of ATO and ATRA should be considered as standard of care in the front-line management of non-high-risk APL. Further studies are needed to evaluate whether this combination is also suitable for the management of other situations, e.g. high-risk APL.

Key messages for clinical practice

1. Suspected APL needs immediate therapy with ATRA and/or ATO without waiting for genetic confirmation.
2. Aggressive supportive care and surveillance is strongly recommended.
3. Diagnostic confirmation at genetic level is mandatory.

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