



Management of Acute Promyelocytic Leukemia

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8.1 Introduction

Acute promyelocytic leukemia (APL), characterized by the balanced translocation t(15;17)(q22;q12) resulting in the fusion transcript *PML-RARA*, is a rare entity of acute myeloid leukemia (AML), accounting for roughly 5–8% of AML patients (Swerdlow et al. 2017). According to the prior French-American-British (FAB) classification, APL was designated as “M3 leukemia” (Bennett et al. 1985) and is now assigned to the World Health Organization (WHO) defined type of AML with recurrent cytogenetic abnormalities, “acute promyelocytic leukemia with t(15;17)(q22;q12), (*PML-RARA*) and variants” (Swerdlow et al. 2017). According to the current WHO classification, patients with specific cytogenetic and molecular genetic abnormalities such as t(15;17)(q22;q12)/*PML-RARA* are classified as AML independently of the

percentage of blast cells in the bone marrow and peripheral blood (Swerdlow et al. 2017).

Detection of the *PML-RARA* fusion is carried out by conventional cytogenetics including fluorescence in situ hybridization (FISH) and/or reverse transcriptase polymerase chain reaction (RT-PCR). Alternative fusion partners are the zinc finger gene (*PLZF*), the nucleophosmin gene (*NPM*), the nuclear mitotic apparatus (*NUMA*) or the *STAT5b* gene (Grimwade et al. 2000). These fusion partners are therapeutically relevant, since the alternative fusion partner involving the *PLZF* gene (t(11;17)(q23;q21)) is not sensitive to all-trans retinoic acid (ATRA) (Redner 2002).

8.2 Diagnostic Work-Up

The vast majority of APL patients mostly display a characteristic abnormal hypergranulation of blast cells and or promyelocytes (Fig. 8.1a) (Swerdlow et al. 2017). Thus, rapid morphological evaluation of peripheral blood as well as bone marrow is mandatory if an APL is suspected. The nuclei of the cells vary in shape and size, being often bilobulated and kidney-shaped (Fig. 8.1b). The cytoplasm of the cells is completely filled with dense and partially condensed granulation. In some cells the cytoplasm is filled with dust granulation. Cells with characteristic bundles of Auer rods are found in the bone marrow or in the peripheral blood, the so-called

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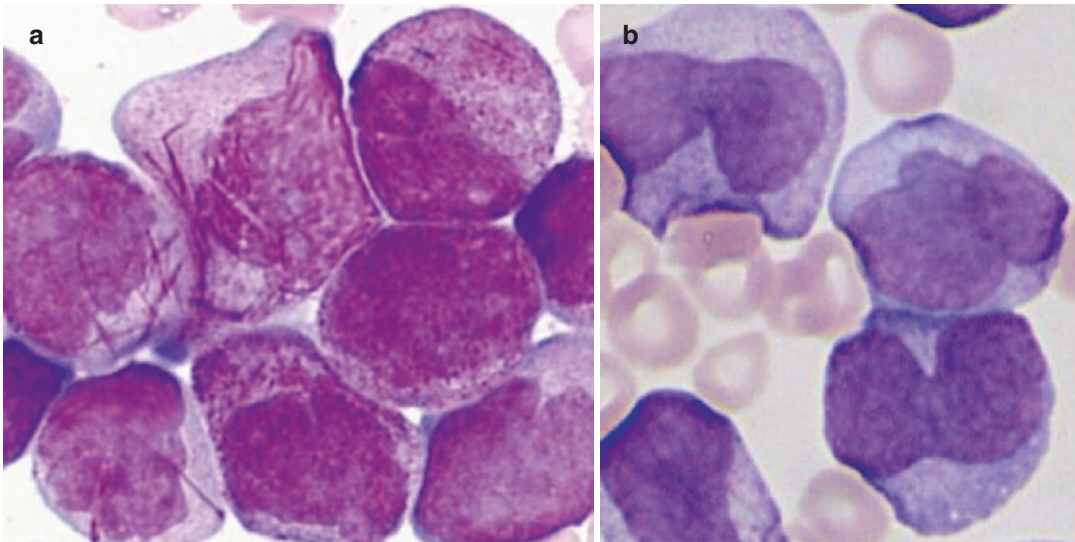


Fig. 8.1 (a) Promyelocytes with characteristic Auer rods/Fagott cells in the cytoplasm. Fagott cells are cells normally found in the hypergranular form of APL (FAB-M3). The promyelocytes have numerous Auer rods in the

cytoplasm which gives the appearance of a bundle of sticks. (b) Bilobulated and kidney-shaped blast cells which are characteristic for the microgranular variant (FAB M3v) of APL

Table 8.1 Overview of the characteristics of the two APL variants

Morphology	FAB M3 hypergranular	FAB M3v microgranular variant
Relative incidence (%)	90–95	5–10
Morphology	<ul style="list-style-type: none"> • Large blast cells • Auer rods, often in bundles • Fagott cells 	<ul style="list-style-type: none"> • Microgranular • Bilobulated and kidney-shaped blast cells
Immunophenotype	CD2 ⁻ ,CD13 ⁺ ,CD33 ⁺ ,CD34 ⁻ ,CD117 ⁺ ,HLA-DR ⁻	CD2 ⁺ ,CD13 ⁺ ,CD33 ⁺ ,CD34 ^{-/+} ,CD117 ⁺ ,HLA-DR ⁻

Fagott cells. The M3 variant (M3v), however, contains fewer cells with hypergranulations or bundles of Auer rods.

Hypergranulated promyelocytes strongly react with POX, SSB, and chloroacetate esterase. The expression of CD33, CD117, and absence of HLA-DR and CD34 on the surface of APL blasts is characteristic of the disease (Table 8.1). The t(15;17) translocation and the respective *PML-RARA* fusion transcript are diagnostically conclusive and represent definitive hallmarks of APL diagnosis (Swerdlow et al. 2017). The molecular analysis for the detection of *PML-RARA* is carried out by either RT-PCR or by FISH. Whereas both methods are used as a fast and highly sensitive verification of the initial diagnosis, only RT-qPCR is sensitive enough for the measurement of measurable residual disease (MRD) in

the course of APL therapy. The results of several independent studies have shown that RT-qPCR positivity for *PML-RARA* transcripts during morphological remission within consolidation cycles is a predictive factor for an early hematological recurrence, whereas RT-qPCR negativity in the bone marrow is usually associated with long-term survival and cure after therapy (also in patients with relapse) (Burnett et al. 1999; Mandelli et al. 1997; Schnittger et al. 2003; Cicconi et al. 2018).

8.2.1 Diagnostic Examination Schedule

Morphological analyses of bone marrow and peripheral blood are recommended at the following time points:

- at initial diagnosis
- after induction
- prior to the second and following consolidation therapy
- after the last consolidation therapy
- quarterly during maintenance therapy in high-risk patients
- after therapy quarterly during a 3 years follow-up from start of therapy
- At suspected relapse

Cytogenetic and immunophenotypic analyses should be performed at diagnosis and in case of relapse.

Molecular analyses with RT-qPCR for evaluation of MRD are recommended according to the risk-status at diagnosis as indicated in Table 8.2.

8.3 Treatment

APL must be classified as an emergency with immediate initiation of treatment with all-trans retinoic acid (ATRA) 45 mg/m²/day as well as supportive therapy. Even when APL is only suspected based on clinical and morphological findings, therapy must be started immediately before a genetic diagnosis is available due to the potential lethal complications and the potential for cure. Prior to therapy, bone marrow and blood diagnostics are essential. Treatment with ATRA has revolutionized improved therapeutic success

in APL, providing the prime example of molecularly targeted treatment (Huang et al. 1988; Tallman et al. 1997). ATRA causes differentiation of abnormal promyelocytes to mature neutrophils in vitro and in vivo. Complete remissions (CR) were achieved with single-agent ATRA in up to 80–90% of newly diagnosed and relapsed APL patients (Huang et al. 1988; Tallman et al. 1997; Ablain and de The 2011; Castaigne et al. 1990; Chen et al. 1991; Chomienne et al. 1990). Additionally, treatment with ATRA abrogates the disturbed coagulation cascade. However, the accelerated differentiation to mature neutrophils often induces a rapid WBC increase. In fact, in 15–20% of patients, the so-called “differentiation-syndrome” (DS) occurs, consisting of, for example, weight gain, respiratory distress, unexplained fever, interstitial pulmonary infiltrates, pleural or pericardial effusions with or without leukocytosis. This syndrome is associated with a high mortality rate (Fenaux et al. 1992; Frankel et al. 1992, 1994; Warrell et al. 1994); specific treatment to overcome DS is discussed in Chap. 4.

Unfortunately, remissions after single agent treatment with ATRA in most of the patients were not sustained (Huang et al. 1988; Tallman et al. 1997; Ablain and de The 2011; Castaigne et al. 1990; Chen et al. 1991; Chomienne et al. 1990). These findings led to the concurrent use of ATRA with chemotherapy (CTX; either an anthracycline plus cytarabine or an anthracycline alone) as the standard of care for induction in newly diagnosed APL (Coombs et al.

Table 8.2 Molecular analyses with RT-qPCR for evaluation of measureable residual disease according to the risk-status at diagnosis

Time point	Low-/intermediate-risk (WBC ≤ 10 × 10 ⁹ /L)	High-risk (WBC > 10 × 10 ⁹ /L)
At initial diagnosis	✓	✓
After induction	–	✓
Prior to the second and following consolidation therapy	–	✓
After the last consolidation therapy	✓	✓
Quarterly during maintenance therapy ^a	–	✓
After therapy quarterly during a 3 year follow-up from start of therapy ^a	–	✓
At suspected relapse	✓	✓

Abbreviation: WBC, white blood cell count

^aPeripheral blood is sufficient for measureable residual disease analysis

2015). More recently, the combination of arsenic trioxide (ATO) with ATRA has been shown to be a very effective CTX-free treatment strategy in de novo, low-/intermediate-risk (low-/intermediate-risk: $WBC \leq 10.0 \times 10^9/l$; high-risk: $WBC > 10.0 \times 10^9/l$) APL (Estey et al. 2006).

In addition, published data of a large multicenter phase 3 randomized trial on the direct comparison of ATO/ATRA vs ATRA in combination with idarubicin (AIDA) or mitoxantrone in adult patients with de novo, non-high-risk APL showed very promising results in favor of ATO/ATRA, with a 2-year event-free survival (EFS) rate of 97 vs 86% ($P = 0.02$) (Lo-Coco et al. 2013). Within this trial, early mortality as well as hematological toxicities were significantly lower in patients treated with ATO/ATRA as compared to AIDA. Particularly, the cumulative incidence of relapse (CIR) after 50 months was only 1.9% after ATO/ATRA as compared to 13.9% after CTX + ATRA (Platzbecker et al. 2016). Moreover, none of the patients treated with ATO/ATRA developed a therapy-related myeloid neoplasm as compared to two patients in the CTX/ATRA arm (Platzbecker et al. 2016). Another publication of the Medical Research Council supports these results, with a 4-year EFS rate of 91% after ATO/ATRA as compared to 70% after CTX/

ATRA ($P = 0.002$) (Burnett et al. 2015). However, the regimen with ATO/ATRA was associated with a higher frequency of grade 3 or 4 hepatic toxicity as compared to CTX/ATRA (44% vs 3%; $P < 0.001$). In all cases, the toxic effects resolved with temporary discontinuation of ATO and/or ATRA (Platzbecker et al. 2016). Taken together, the CTX-free regimen with ATO/ATRA has become standard first-line therapy in non-high-risk de novo APL. Figure 8.2 and Table 8.3 give an overview of the treatment schedule and dosages. We recommend the following approach:

- prophylaxis of differentiation syndrome with prednisone 0.5 mg/kg/day p.o. from day 1 of ATO application to the end of induction therapy as well as hydroxyurea (see Chap. 4, Sect. 4.3) if WBC count raises up to $>10 \times 10^9/L$
- bone marrow evaluation on day 28
- induction therapy should be terminated on the basis of morphological criteria (if CR or CRi is reached on day 28)
- in case CR or CRi is not achieved by day 28, ATO/ATRA therapy should be continued up to max. day 60 until terminal differentiation is reached; this should be accompanied by serial bone marrow assessments to definitively demonstrate CR

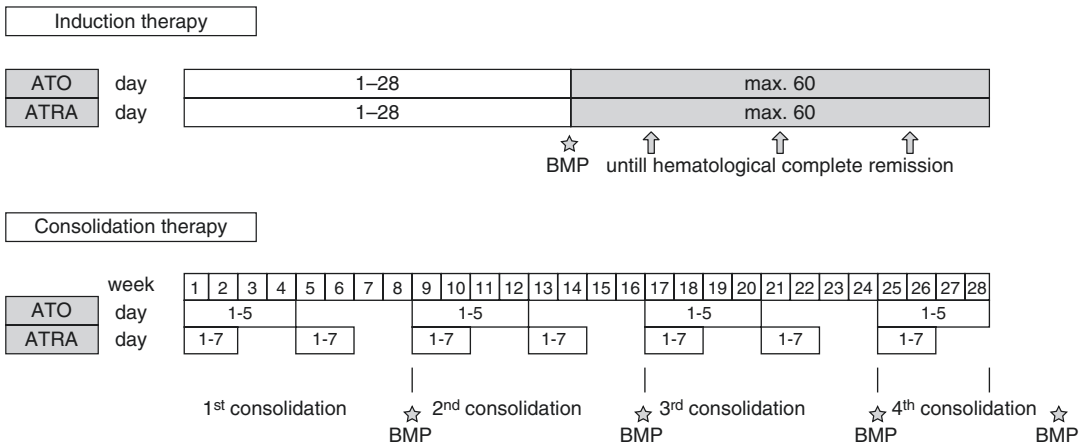


Fig. 8.2 Treatment recommendation for non-high-risk APL ($WBC \leq 10 \times 10^9$ at diagnosis) according to the APL0406 study

Table 8.3 Treatment schedule and dosages of arsenic trioxide and all-trans retinoic acid as first-line therapy in non-high-risk acute promyelocytic leukemia

Drug	Dose	Route	Administration
<i>Induction</i>			
ATO	0.15 mg/kg	Intravenously	Over 2 h daily starting on day 1, until CR, maximally 60 days
ATRA	45 mg/m ²	Per os	In two single doses daily starting on day 1, until CR, maximally 60 days; doses will be rounded-up to next 10 mg increment
<i>Consolidation</i>			
ATO	0.15 mg/kg	Intravenously	Over 2 h daily for 5 days a week; treatment break on day 6 and 7 4 weeks on 4 weeks off for a total of 4 courses; last cycles will be administered on week 25–28
ATRA	45 mg/m ²	Per os	In two single doses daily 14 days on, 14 days off for a total of 7 courses; doses will be rounded-up to next 10 mg increment

ATO arsenic trioxide, ATRA all-trans retinoic acid

- cytogenetic and molecular assessment at the end of induction therapy has no value in case of CR. Molecular responses should be assessed after consolidation only

ATO/ATRA-based induction therapy is followed by 4 courses of ATO/ATRA-based consolidation. Start of consolidation cycles is considered after hematological recovery with neutrophils $\geq 1.0 \times 10^9/L$ and platelets $\geq 100 \times 10^9/L$. In case of morphological CR and hematological recovery, consolidation therapy should be started within 4 weeks after documented CR. Each course of therapy should be initiated at hematological recovery from the previous course. The PCR status after the end of consolidation is an important stratification parameter for the subsequent therapy. However, it needs to be mentioned that the rate of molecular remission was 100% after ATO/ATRA in the pivotal study (Platzbecker et al. 2016).

During all consolidation cycles (Swerdlow et al. 2017; Bennett et al. 1985; Grimwade et al. 2000; Redner 2002) the following diagnostics are recommended:

- bone marrow samples should be collected after full hematological recovery prior to the start of the second, third, and fourth consoli-

dation cycle as well as after the last consolidation cycle and should be tested for morphology and by RT-qPCR for assessment of molecular remission

- patients without molecular remission at the end of all consolidation cycles are very rare cases (<1%) and will be considered molecularly resistant and should be offered conventional chemotherapy (e.g., AIDA) followed by an autologous or allogeneic hematopoietic stem cell transplantation

In countries where ATO is not yet available AIDA-based CTX is still the standard.

8.3.1 Dose Modifications

In case of non-hematological toxicities (grade 3/4 toxicities according to CTCAE Version 4.03) of ATO and ATRA (e.g., QT prolongation, differentiation syndrome, hepatotoxicity, pseudotumor cerebri) dose modifications according to Table 8.4 are recommended. As soon as the symptoms and the patients' clinical conditions improve, treatment with ATRA and/or ATO should be resumed at 50% of the previous dose during the first 7 days after the disappearance of the symptoms. Thereafter, in the absence of

Table 8.4 Dose modifications in case of non-hematological toxicities

Dose level	0 (Start level)	-1	-2	-3
ATO (mg/kg)	0.15	0.11	0.10	0.075
ATRA (mg/m ²)	45	37.5	25	20

ATO arsenic trioxide, ATRA all-trans retinoic acid

worsening of the previous toxicity, ATRA and/or ATO should be resumed at full dosage. In case of the reappearance of symptoms, ATRA and ATO should be reduced to the previous dosage.

8.4 Supportive Measures and Management of Complications

8.4.1 Treatment of Coagulopathy

APL is typically associated with frequently life-threatening hemorrhagic diathesis, which is attributed to a disseminated intravascular coagulation-like coagulopathy (Swerdlow et al. 2017; Tallman and Kwaan 1992; Sanz and Montesinos 2010). The pathogenesis of hemorrhagic complications in patients with APL is complex, often triggered by higher white blood cell (WBC) counts and includes factors of blood coagulation and fibrinolysis such as severe hypofibrinogenemia, increased levels of fibrin degradation products, or D-dimers combined with a prolonged prothrombin or activated partial thromboplastin time as well as thrombocytopenia (Mantha et al. 2016). The hemorrhagic diathesis is one of the main causes of early death (ED) in APL patients (Sanz and Montesinos 2010; Mantha et al. 2016). Release and exposure of tissue factor and annexin II by the leukemic blasts are triggering these processes. Thus, the absolute WBC count, reflecting the absolute leukemic mass, seems to correlate with the severity of bleeding complications (Mantha et al. 2016).

Before the ATRA era, the risk of early hemorrhagic death for newly diagnosed patients with APL was up to 20% and decreased to 5–10% after introduction of ATRA in 1988 (Rodeghiero et al. 1990). Therefore, current guidelines advise

to start ATRA as soon as the diagnosis of APL is suspected to treat and prevent hemorrhagic complications (Sanz et al. 2009). However, it must be noted that the therapy with ATRA can result in a reversion of the clotting disorder into a thrombophilic constellation with thromboembolic events. The benefit of heparin, tranexamic acid, or other anticoagulant or anti-fibrinolytic therapy to attenuate the thrombohemorrhagic risk remains questionable. In a historical comparison of the LPA99 with the LPA96 trials, the use of tranexamic acid had no impact on decreasing the hemorrhagic mortality (Sanz and Montesinos 2010). Additionally, the role of factor VIIa or prothrombotic complex concentrates for treating life-threatening hemorrhages in APL remains uncertain. Although there are case reports in which the use of recombinant factor VIIa was effective for the treatment of life-threatening hemorrhage in patients with APL (Zver et al. 2004; Alimoghaddam et al. 2006), theoretically these agents may enhance the thrombotic risk (Mantha et al. 2016; Rodeghiero et al. 1990). Therefore, the prophylactic use of anticoagulant, antifibrinolytic, or procoagulant agents should be restricted to clinical trials. Finally, any invasive procedures, including the insertion of central intravenous catheters as well as other procedures (e.g., bronchoscopy or lumbar puncture), should be avoided until coagulopathy has resolved (Sanz et al. 2009). Supportive therapy to counteract the coagulopathy should be initiated in parallel to APL-specific treatment. This includes the application of fibrinogen as well as platelet transfusions to maintain fibrinogen concentration above 100 mg/dL and platelet count as high as possible ($>50 \times 10^9/L$) but at least above $30 \times 10^9/L$, respectively (Sanz et al. 2009). In case of unavailability of pure fibrinogen preparation, a substitution with fresh frozen plasma is indicated.

Only limited data exist about the effect on hemorrhagic risk by the addition of ATO to induction therapy. There was no case of early hemorrhagic death in the ATO/ATRA-arm for patients with low-/intermediate-risk (pretreatment $WBC \leq 10 \times 10^9/L$) disease within the APL0406 trial (Lo-Coco et al. 2013). Nevertheless, in high-

risk patients, CTX (preferably idarubicin) in combination with ATRA should be initiated as early as possible to terminate the perilous bleeding cascade.

8.4.2 Therapy of Differentiation Syndrome

DS is a complication during induction caused by the differentiating effects of ATRA and/or ATO on leukemic blasts, which can be fatal if not treated (Sanz and Montesinos 2014). Symptoms may include unexplained fever, dyspnea, acute respiratory distress, interstitial pulmonary infiltrates, pleural or pericardial effusions, weight gain or peripheral edema, hypotension, and renal, hepatic, or multi-organ dysfunction. Leukocytosis frequently but not always accompanies DS and often precedes its clinical manifestations (Montesinos et al. 2009a).

If DS is suspected, 10 mg dexamethasone twice daily intravenously, concomitant diuretic therapy and hemodynamic monitoring should immediately be initiated until resolution of signs and symptoms. Temporary discontinuation of ATRA and/or ATO may be required in cases of severe DS (Sanz et al. 2009). Early transfer of patients to an intermediate care unit for improved monitoring of vital signs should be considered. As soon as the patients' clinical condition improves, the symptoms have disappeared and the WBC count is sustainably lowered to $<10 \times 10^9/L$, the APL treatment with ATRA and/or ATO can be resumed at 50% of the previous dose during the first 7 days. ATRA and/or ATO might be resumed at full dosage in the absence of worsening of the previous toxicity. In case of reappearance of the previous symptoms, ATRA and ATO should be reduced to the previous dosage. The evidence for the use of corticosteroids as a prophylactic approach to prevent DS, however, is limited. Within the APL2000 trial, the DS-related death rate decreased from 5.7 to 3.9% in high-risk patients after the prophylactic use of dexamethasone as compared to the earlier APL93 trial, in which prophylactic dexamethasone was not used (Sanz and Montesinos

2010; Kelaidi et al. 2009). Within the APL0406 trial, prednisone was given prophylactically at a dose of 0.5 mg/kg/day from day 1 until the end of induction therapy (Lo-Coco et al. 2013). DS developed in 19% in the ATO/ATRA group and in 16% in the CTX/ATRA group, but was fatal in only 2.5% assigned to CTX/ATRA (Lo-Coco et al. 2013). Based on these results, we recommend prednisone prophylaxis as done in the APL0406 trial.

8.4.3 Treatment of Leukocytosis During Induction

Leukocytosis commonly occurs, either at initial presentation or during therapy in patients treated with ATRA and/or ATO induction as a result of DS. Thus, in low-risk APL, hydroxyurea 500 mg once/daily for WBC between 10 and $20 \times 10^9/L$, 500 mg twice/daily for WBC between 21 and $50 \times 10^9/L$, and 1.000 mg twice daily above $50 \times 10^9/L$ should be used in case of leukocytosis and should be continued at a given dose to keep the WBC count $<10 \times 10^9/L$ and subsequently tapered (Table 8.5) (Lo-Coco et al. 2013). Additionally, APL cells are sensitive to therapy with anthracyclines. Thus, treatment with anthracyclines such as idarubicin should be considered as early as possible during induction therapy of high-risk patients. ATO/ATRA in combination with idarubicin was used up-front within the phase 2 APML4 trial, in part to prevent hyperleukocytosis and DS (Iland et al. 2012). In this trial, no deaths from DS occurred. Furthermore, gemtuzumab ozogamicin (GO) was successfully used within the AML17 trial in high-risk patients to control leukocytosis (Burnett et al. 2015).

Table 8.5 Treatment of leukocytosis in low-/intermediate-risk acute promyelocytic leukemia during induction therapy due to differentiation syndrome

White blood cell count $\times 10^9/L$	Hydroxyurea
10–20	500 mg/daily
21–50	500 mg twice/daily
>50	1.000 mg twice/daily

In contrast, leukapheresis has no role in upfront treatment, and may even be harmful in high-risk patients with leukocytosis, because this procedure may exacerbate the coagulopathy and was associated with a high risk of death (Vahdat et al. 1994).

8.4.4 QT Prolongation Associated with ATO

Treatment with ATO is associated with electrolyte abnormalities and prolongation of the QT interval corrected for the heart rate (QTc), which can lead to ventricular tachycardia with fatal outcome (Barbey et al. 2003; Unnikrishnan et al. 2004). Prolongation of the QTc interval occurred in 12 of 77 (16%) patients in the ATO/ATRA group within the APL0406 trial and was severe (QTc \geq 501 ms) in one patient. Therefore, close monitoring of the electrocardiogram and electrolytes is necessary during treatment with ATO. Particularly, magnesium and potassium levels should always be kept within the upper-normal range. Concomitant therapy with drugs that are known to prolong the QTc interval should be discontinued. In patients with an absolute QTc interval $>$ 500 ms, ATO should be discontinued, ideally together with any QTc prolonging medication, and electrolytes should be repleted. The time between discontinuing ATO and normalization of the QTc interval may take several days. Once QTc is normalized, ATO should be continued at 0.075 mg/kg (50%) for the first 7 days, and, if no further prolongation occurs, ATO should be escalated to 0.11 mg/kg for a second week. Thereafter, if no prolongation occurs, ATO could be continued at full dose (Lo-Coco et al. 2013).

8.4.5 Pseudotumor cerebri with ATRA Therapy

A “pseudotumor cerebri,” manifesting with headaches, nausea, vomiting, and blurred vision, may occur during ATRA therapy, particularly in younger patients. It is recommended to

discontinue ATRA treatment temporarily and to administer pain killers. As soon as the symptoms and the patients’ clinical conditions improve, the treatment with ATRA should be resumed at 50% of the previous dose during the first 7 days. In the absence of worsening of the previous toxicity, ATRA should be resumed at full dosage thereafter.

8.4.6 Long-Term Toxicities with ATO/ATRA

The up-front use of ATO/ATRA is anticipated to reduce the long-term toxicities associated with anthracycline therapy. However, studies indicate that potential long-term complications exist. In one long-term follow-up study among 265 newly diagnosed APL patients treated with ATO/ATRA between 2001 and 2012, with a median follow-up of 83 months, higher rates of grade 1 liver dysfunction (15% vs 2%) and hepatic steatosis (43% vs 18%) were seen as compared to healthy controls (Zhu et al. 2016). Breast cancer developed in one patient 3 years after termination of ATO. Eight patients developed hyper-, or hypopigmentation, or hyperkeratosis/hyperplasia. All skin lesions occurred during maintenance therapy or within 6 months after treatment, and patients recovered within 2 to 18 months (Zhu et al. 2016). However, the common signs of chronic arseniasis, such as cardiovascular events, chronic renal insufficiency, diabetes, or neurological dysfunction, were not observed (Zhu et al. 2016). In some cases, peripheral neuropathy has been reported during and after treatment with ATO (Kühn et al. 2016; Shigeno et al. 2005). Symptoms are usually mild and reversible following discontinuation of treatment, but may be severe and irreversible in patients with coexistence of thiamine deficiency (Kühn et al. 2016).

Further evidence suggests a high frequency of varicella zoster virus (VZV) reactivation after ATO-based treatment. In a publication by Yamakura et al. VZV reactivation occurred in seven (46.7%) of 15 patients after ATO-based treatment as compared to none in ten patients

treated with conventional CTX. All patients responded promptly to treatment with acyclovir or valacyclovir and did not develop postherpetic neuralgia. Thus, we recommend the prophylactic use of acyclovir or valacyclovir throughout ATO-based therapy (Yamakura et al. 2014).

Very recently, Norsworthy et al. reported data of 124 adult APL patients from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute who were diagnosed with APL between 2006 and 2015 (Norsworthy et al. 2019). The authors performed an exploratory population-based analysis of secondary malignancies in patients treated with or without ATO. This exploratory analysis revealed a higher incidence of second malignancies in APL patients treated with ATO, although the risk was not significantly increased compared to patients who received other APL therapies (9.9% vs 6.0% at 24 months, $P = 0.24$). Despite that, survival outcomes appeared better after ATO-based therapy (Norsworthy et al. 2019). However, the analyses were limited by a small sample size, short follow-up, potential selection and immortal time bias, and unaccounted for differences between comparator groups.

Based on this limited data, no firm conclusions can be drawn regarding the occurrence of comorbidities and organ toxicities. However, we suggest routine follow-up to monitor for and manage cardiovascular risk factors. Finally, age-appropriate cancer screening should be emphasized in all patients after completion of APL therapy.

8.5 Treatment of High-Risk APL

Patients with high-risk APL account for roughly 30% of patients. After induction treatment with AIDA, subsequent risk-guided consolidation cycles have shown to equalize the risk of relapse between both APL risk groups based on initial WBC counts (Sanz et al. 2000, 2004a). Due to its success in *de novo* non-high-risk APL (Lo-Coco et al. 2013), ATO/ATRA has also been explored as front-line use in high-risk APL. However, phase 2 studies have demonstrated lower CR

rates with single agent ATO ± ATRA as compared to classical AIDA-based induction regimens in high-risk patients (Estey et al. 2006; Sanz et al. 2000, 2004a; Ghavamzadeh et al. 2011; Mathews et al. 2006; Ravandi et al. 2009).

Recently, Abaza et al. published outcome data on 187 APL patients, including 54 with high-risk APL (Abaza et al. 2017). In an attempt to improve outcomes in high-risk patients, they added GO ($n=45$) or idarubicin ($n=7$) to ATO/ATRA. Albeit results were drawn from a small cohort, 5-year overall survival (OS) were not significantly different between the two treatment arms (84% vs 100%; $P = 0.45$) and are in-line reported by others (Estey et al. 2006; Ravandi et al. 2009). Similar results were reported by Burnett et al. on the phase-3 AML17 trial comparing ATO/ATRA with CTX/ATRA in newly diagnosed patients with APL (Burnett et al. 2015). High-risk patients treated with ATO/ATRA received one initial dose of GO (6 mg/m²). The 4-year EFS-rate was 91% after ATO/ATRA/GO as compared to 70% in the CTX/ATRA group. Furthermore, the cumulative incidence of morphological and molecular relapses were reduced from 18% and 27% in the CTX/ATRA group to 1% and 0% in the ATO/ATRA/GO group (Burnett et al. 2015). Currently, the European randomized intergroup study “APOLLO” investigates idarubicin 12 mg/m² on days 1 and 3 in addition to oral ATRA 45 mg/m² twice daily on days 1–28 and ATO 0.15 mg/kg/day intravenously on days 5–28 followed by four cycles of ATO/ATRA consolidation therapy as compared to the standard CTX/ATRA approach (ClinicalTrials.gov identifier: NCT02688140).

In patients with high-risk APL, treatment with idarubicin + ATRA should be started as soon as possible. After achieving a hematological CR, three consolidation cycles of ATRA plus either idarubicin/cytarabine (course 1 and 3) or plus mitoxantrone (course 2) are intended (Norsworthy et al. 2019). This approach is also supported by published data combining intensive CTX according to the 7 + 3 scheme and ATRA (Lengfelder et al. 2009). Moreover, a positive impact of adding ATO to consolidation regimens was reported for all risk groups of APL in the C9710 trial (Powell et al. 2010). The efficacy of

ATO as consolidation therapy was recently confirmed by Lou et al., who reported that treatment with ATO as post-remission therapy significantly improved long-term outcome as compared to standard CTX (Lou et al. 2014).

Thus, ATO as consolidation therapy in high-risk patients could be considered, although currently not authority approved.

8.6 Maintenance Therapy

8.6.1 Maintenance in Patients with High-Risk APL

The clinical benefit of maintenance therapy particularly in patients with negative MRD is still discussed controversial due to adverse side effects (AEs) including cytopenia and/or increase of the liver values. In the European APL-93 study, triple-agent maintenance therapy with ATRA, 6-mercaptopurine (6-MP) and methotrexate (MTX) resulted in a lower recurrence rate, particularly in patients with high-risk (Fenaux et al. 1999). However, this study did not differentiate between patients according to the MRD status after consolidation. Several other publications also demonstrated that an ATRA-based maintenance is needed after consolidation to ameliorate survival (Tallman et al. 1997, 2002; Kantarjian et al. 1987; Adès et al. 2010). In contrast, patients randomized to maintenance therapy with 6-MP and MTX in the LAP 0389 study did not have better outcomes than those randomized to observation, which is in line with recently published results (Avvisati et al. 2002, 2011; Asou et al. 2007). It is currently unclear, if maintenance therapy further enhances the risk for secondary malignancies, including therapy-related myeloid neoplasm. Within the recently published long-term follow-up data of the LPA96&99 as well as LPA2005 trials, 24 patients (11%) developed a secondary neoplasm in CR within a median time of 51 months (range, 6–112 months; 11 solid tumors and 7 therapy-related myeloid neoplasms within the LPA96&99 trials; 3 solid tumors and 3 therapy-related myeloid neoplasms within the LPA2005 trial,

respectively) (Martínez-Cuadrón et al. 2018). Twenty-one patients died because of the secondary neoplasm. Cumulative incidence of secondary neoplasms at 5 and 10 years was 8% and 16%, respectively. However, the authors stated that no predictive factors for this event were found (Martínez-Cuadrón et al. 2018).

Taken together, maintenance therapy may still play a role in patients with high-risk receiving CTX/ATRA while its omission in the setting of ATRA and ATO is currently under investigation.

8.6.2 ATO as Maintenance Therapy

Treatment with oral ATO was shown to be well absorbed and to achieve a bioavailability of up to 95% of an equivalent dose of intravenous ATO (Kumana et al. 2002). Since slow oral absorption results in lower peak plasma arsenic levels compared with intravenous ATO, the oral formulation is associated with minimal prolongation of the QT interval (Siu et al. 2006; Kwong et al. 2001). Thus, a home-based treatment without the need of daily hospital visits and monitoring for QT prolongation or cardiac arrhythmias seems to be feasible.

Recently, Au et al. have published 10-year follow-up data on outcome after oral ATO-based maintenance therapy (Au et al. 2011). Seventy-six APL patients in first CR after induction and consolidation with daunorubicin/cytarabine received oral maintenance therapy with ATO ± ATRA or ATO/ATRA/ascorbic acid, given for 2 weeks every 2 months for 2 years. Prolonged oral ATO maintenance was feasible and safe and resulted in 3-year leukemia-free and OS of 87.7% and 90.6%, respectively (Au et al. 2011).

Taken together, maintenance treatment has been mainly used in CTX/ATRA regimen. Based on the results of the APL0406 trial, it seems that using the CTX-free regimen in low-risk APL, no maintenance was needed (Lo-Coco et al. 2013). In contrast, in high-risk APL treated with CTX/ATRA, maintenance might still play a role, particularly in MRD positive patients. Thus, maintenance therapy is included in the majority of protocols based on CTX/ATRA and, so far,

still recommended for high-risk patients after an AIDA-based therapy in the absence of toxicities.

8.6.3 Treatment of Elderly Patients

Although it is generally noted that APL seems to be rather uncommon in elderly patients (Sanz et al. 2009), its true incidence in this age cohort is unclear, particularly in patients beyond the age of 70 years. According to a population-based report from the Swedish adult acute leukemia registry, the proportion of patients with APL decreased significantly with age from 17% in patients younger than 30 years to 0.9% in patients 80 years and older (Lehmann et al. 2011). In addition, since comorbidities are more common in elderly patients, these patients are less likely to be admitted to a hematological department. More importantly, ED rate after ATRA ± anthracycline-based induction therapy was 60% in patients above the age of 80 years as compared to 18.8% in patients aged 50–59 years. ED was associated with poor performance status, explaining the high rate in very elderly patients (Lehmann et al. 2011). A previous report on 104 elderly (median age, 68 years; range, 60–83 years) patients showed that older patients could be successfully treated using ATRA plus anthracycline for induction and consolidation (Sanz et al. 2004b). Patients who were MRD negative at the end of consolidation received oral 6-mercaptopurine (50 mg/m²/day), intramuscular methotrexate (15 mg/m²/week), and ATRA (45 mg/m²/day for 15 days every 3 months) over 2 years as maintenance therapy. Overall, outcome was favorable with an ED-rate of 15%, CR-rate of 84%, a 6-year CIR of 8.5%, and disease-free survival (DFS) of 79%, respectively (Sanz et al. 2004b). However, the CR-rate was lower in patients older than 70 years as compared to patients aged 60–70 years (74% vs 89%) (Sanz et al. 2004b). These results had recently been confirmed by Martínez-Cuadrón et al. comparing the long-term outcome of older patients (median age, 67 years) with de novo APL treated within the LPA2005 vs LPA96&99 trials (Martínez-Cuadrón et al. 2018). The LPA2005 trial, which

was based on an age- and risk-adapted therapy with reduced post-consolidation CTX, resulted in a higher 5-year DFS (87% vs 69%; $P = 0.04$) and 5-year OS (74% vs 60%; $P = 0.06$) as compared to the LPA96&99 trials (Martínez-Cuadrón et al. 2018).

However, contrary results were published recently by Lengfelder et al. who reported on 91 newly diagnosed APL patients (median age, 67 years) registered by the German AML Cooperative Group between 1994 and 2011 (Lengfelder et al. 2013). Overall, 75% of the patients were treated on clinical trials, but the 25% non-eligibility rate was remarkably high, attributable to multimorbidity and low performance status. Fifty-six patients received induction therapy with ATRA and 6-thioguanine, cytarabine, daunorubicin (TAD), and consolidation and maintenance therapy. Treatment intensification with a second induction cycle (high dose cytarabine and mitoxantrone, (HAM)) was optional ($n = 14$). The 7-year OS, EFS and relapse-free survival (RFS) were 45%, 40%, and 48%, respectively. In patients treated with TAD-HAM induction, 7-year RFS was superior (83%; $P = 0.006$) compared to TAD only, and no relapse was observed. Thus, intensified induction therapy seemed to be highly effective, but was restricted to a selection of those patients, who could be treated intensively, since elderly patients have a higher vulnerability to treatment toxicity (Lengfelder et al. 2013). Sanz et al. noted that 6 of 25 (24%) patients ≥ 70 years died in remission (Sanz et al. 2004b), while Ades et al. reported that 19% of patients ≥ 60 years died due to complications of myelosuppression during consolidation with daunorubicin/cytarabine (Ades et al. 2005). Therefore, a higher vulnerability to treatment toxicities in older patients may result in a higher treatment-related mortality.

Regarding the distribution of risk-category according to WBC count at diagnosis, published data are again contradictory (Sanz et al. 2004b; Lengfelder et al. 2013). Sanz et al. reported that older patients seem to be more likely to present with non-high-risk APL as compared to their younger counterparts (37% vs 18%), which in

part may account for the low relapse rate observed in their publication (Sanz et al. 2004b). In contrast, Lengfelder et al. reported on 31% ($n = 28/91$) of patients with high-risk APL (Lengfelder et al. 2013).

Regarding outcome after ATO/ATRA in elderly patients, data are scarce also since age limit in the pivotal APL0406 trial was 70 years and only a very low number of patients above 60 years were included (Lo-Coco et al. 2013). On the other side, there is no evidence to assume that the biology of non-high-risk APL in the elderly might be different as compared to younger APL patients. Zhang et al. reported on 33 *de novo* APL patients with a median age of 65 years (range, 60–79 years) treated with single-agent ATO for remission induction and consolidation therapy (Zhang et al. 2013). The CR-rate was 88% and the ED-rate 12%. The 10-year CIR-, OS-, and DFS-rates were 10.3%, 69.3%, and 64.8%, respectively. Overall, monotherapy with ATO was well tolerated with leukocytosis (64%) being the most common adverse event during induction, whereas non-hematological adverse events were all manageable and reversible. In addition, non-relapse mortality (NRM) was only 6.9% after monotherapy with ATO due to noninfectious diseases (Zhang et al. 2013) as compared to 10–18.6% despite reduced intensities of CTX in older patients, mainly due to infection (Ades et al. 2005; Mandelli et al. 2003; Disperati et al. 2007). None of the patients treated with ATO developed a secondary malignancy with the exception of one patient who had longstanding hepatitis B virus infection and hepatic cirrhosis, and died of liver cancer 117 months after achievement of CR (Zhang et al. 2013). Very recently, we have evaluated the outcome of 433 elderly patients (median age, 73.4 years) treated either with CTX/ATRA or ATO-based therapy (Kayser et al. 2020). CR was achieved in 92% after therapy with ATO/ATRA and in 82% after CTX/ATRA; induction death rates were 8% and 18%, respectively. CIR was significantly lower after ATO/ATRA \pm CTX as compared to CTX/ATRA ($P < 0.001$) (Kayser et al. 2020). High ($>10 \times 10^9/L$) WBC counts at diagnosis were associated with higher CIR ($P < 0.001$) as com-

pared to lower WBC in the CTX/ATRA group, but not in the ATO/ATRA \pm CTX group ($P = 0.48$). Thus, it seems reasonable to offer ATO/ATRA \pm CTX as first line treatment to older patients irrespective of the risk-group.

8.6.4 Treatment of APL During Pregnancy

The occurrence of APL during pregnancy seems to be rather rare with limited evidence-based information available limited to small retrospective series and case reports. Most reliable data are therefore only available of national and international cancer registry databases (Sanz et al. 2015). Miguel Sanz on behalf of the PETHEMA study group has reported so far on the largest cohort of 14 (0.8%) pregnant women of overall 1.744 APL patients, who had been registered in their database between 1996 and 2012 (Sanz et al. 2015). Besides supportive therapy, the initiation of effective APL treatment to stop coagulopathy is of utmost importance. Table 8.6 provides an overview of fetal and maternal outcome after treatment of pregnant APL patients.

8.6.4.1 Treatment Options During the First Trimester

Overall, therapeutic options are extremely limited during the first or early second trimester in terms of successful outcome of the fetus. Isotretinoin (a compound comparable to ATRA) has been shown to be teratogenic, leading to a range of severe craniofacial, cardiac, and central nervous system abnormalities as well as increased rate of abortions (Lammer et al. 1985; Rosa 1983; Lynberg et al. 1990; Chalmers 1992). In a systematic review by Verma and colleagues of 71 APL patients diagnosed during pregnancy, 23% were diagnosed with APL in the first trimester and 69% of those were treated with ATRA (Verma et al. 2016). Abortion rate, either spontaneously or therapeutically induced, was very high (90%) during the first trimester. Moreover, women in the first trimester were more likely to experience obstetric and fetal

Table 8.6 Fetal and maternal outcome of pregnant patients with acute promyelocytic patients

No. of pregnant women	Treatment	Maternal outcome	Fetal outcome	Reference
71 (systematic review) First trim: 16 Second trim: 20 Third trim: 28 Unk: 7	ATRA/ anthracycline/ AraC: <i>n</i> = 9 ATRA/ anthracycline: <i>n</i> = 30 ATRA: <i>n</i> = 16 Anthracycline/ AraC: <i>n</i> = 10 Others: <i>n</i> = 6	CR: 93% (53/58) Obstetric complications during first as compared to second/third trim: 86.7% vs 15.9% Premature cesarean section or induction of labor: 41% (27/66) Relapses: <i>n</i> = 4 after a median follow-up of 10.5 months; salvage with CTX ± ATRA, 2 deaths due to APL, 1 death due in second CR	Outcome reported of <i>n</i> = 54 Preterm: <i>n</i> = 25 Spontaneous or therapeutic abortion or intrauterine death: <i>n</i> = 18 Fetal complications during first as compared to second/third trim: 92.3% vs 37.5% Complications included: Respiratory distress syndrome: <i>n</i> = 6 oligohydramnios and intrauterine growth retardation: <i>n</i> = 4 Arrhythmias or cardiac issues: <i>n</i> = 3 Mild intraventricular brain hemorrhage: <i>n</i> = 1	Verma et al. <i>Leuk Lymphoma</i> 2016; 57: 616–622
14 First trim: 3 Second trim: 2 Third trim: 7 After delivery: 2	AIDA: 12	CR: 92% (11/12) ED: 2 (due to hemorrhage)	First trim: 5 abortions Second and third trim: Normal development in <i>n</i> = 8, 1 dead fetus (26th week of gestation)	Sanz et al. <i>Ann Hematol</i> 2015; 94: 1357–1361
1 (third trim)	ATRA mono	CR: 100%	Cesarean section after 30 weeks: <i>n</i> = 1	Culligan et al. <i>Clinical Leukaemia</i> 2007; 1: 183–191
1 (second trim)	ATRA/CTX	CR: 100%	Normal, but premature (35th week of gestation)	Giagounidis et al. <i>Eur J Haematol</i> 2000; 64: 267–271
1 (second trim)	ATRA mono (30 days)	CR: 100%	Caesarean section (30 weeks of gestation) Cardiac arrhythmia and sustained cardiac arrest	Harrison et al. <i>Br J Haematol</i> 1994; 86: 681–682
1 (third trim)	ATRA mono	CR: 100% Massive bleeding during delivery (extensive vaginal and perineal rupture)	Normal development	Stentoft et al. <i>Leukemia</i> 1994; 8: 1585–1588
1 (third trim)	ATRA mono for 4 weeks until delivery 2 weeks postpartum: Consolidation cycles with daunorubicin/ AraC	CR: 100%	Induced labor, vaginal delivery, normal development	Lipovsky et al. <i>Br J Haematol</i> 1996; 94: 699–701

(continued)

Table 8.6 (continued)

No. of pregnant women	Treatment	Maternal outcome	Fetal outcome	Reference
1 (second trim)	4 cycles AIDA	CR: 100%	Term delivery (36.7 weeks of gestation), transient mild respiratory distress during the peripartum period, moderate, non-persistent dilation of the right atrium and right ventricle with mildly depressed function, two small secundum atrial septal defects, and a small patent ductus arteriosus	Siu et al. <i>Int J Gynecol Cancer</i> 2002; 12: 399–402
1 (third trim)	ATRA mono until CR consolidation with daunorubicin/ AraC	CR: 100%	Elective cesarean section (33.6 weeks of gestation); retardation of growth and non-persistent blocked atrial premature contractions and arrhythmia, resolving at the next day	Terada et al. <i>Leukemia</i> 1997; 11: 454–455
3 First trim: 1 Third trim: 2	First patient (first trim): AIDA after therapeutic abortion Second patient (third trim): AIDA 1 week after cesarean section Third patient (third trim): ATRA for 2 weeks before delivery	CR: 67% ED: 33% due to ATRA syndrome 1 week after delivery	Normal development	Consoli et al. <i>Int J Hematol</i> 2004; 79: 31–36

AIDA all-trans retinoic acid and idarubicin, AraC cytarabine, ATRA all-trans retinoic acid, CR complete remission, CTX chemotherapy, trim trimester

complications as compared to the subsequent trimesters (Verma et al. 2016). Therefore, ATRA should not be offered to pregnant APL patients during the first trimester, particularly during organogenesis (~8–10 weeks following conception) given the teratogenic potential of ATRA (Lammer et al. 1985; Rosa 1983; Lynberg et al. 1990; Chalmers 1992). Cytarabine and/or anthracyclines are known to increase the risk of spontaneous abortions or cause major malformations by up to 20% (Lishner et al. 2016; Caligiuri 1992; Yang and Hladnik 2009; Williams and Schilsky 2000; Amant 2012).

Thus, the option of therapeutic abortion has to be discussed with the patient, in particular during the first trimester. In cases, in which an abortion is no option, treatment with an anthracycline should be given and combined with ATRA in

early second trimester. Since idarubicin is more lipophilic and may therefore be associated with an increased placental transfer and possible fetotoxicity (Reynoso and Huerta 1994; Ahtari and Hohlfeld 2000), daunorubicin 60 mg/m² should be used for a maximum of three consecutive days. The addition of cytarabine 100–200 mg/m² days 1–7 should be considered during induction and consolidation (Adès et al. 2006), particularly in patients with high-risk APL. CTX alone, however, increases the risk of hemorrhage due to the release of pro-coagulants and plasminogen activators from malignant cells (Sanz and Montesinos 2010).

Moreover, early labor or cesarean section has to be considered the best option as soon as the fetus can be delivered at a viable stage. In addition, CTX with an anthracycline in

combination with ATRA or ATO/ATRA (non-high-risk APL) should be given as soon as possible after delivery.

8.6.4.2 Treatment Options During the Second or Third Trimester

CTX/ATRA after the beginning of the second trimester results in a more successful outcome for the unborn as compared to therapy in the first trimester, since the risk of fetal malformations reduces with advanced stage of pregnancy (Sanz et al. 2015; Claahsen et al. 1998; Consoli et al. 2004; Giagounidis et al. 2000). A high CR-rate of 92% had been reported in 11 of 12 pregnant APL patients treated with AIDA-based induction therapy; one woman died 2 weeks after start of induction therapy due to a DS. All women proceeded to consolidation and maintenance therapy and were reported to be in an ongoing CR after a median follow-up time of 83 months (Verma et al. 2016). In addition, the rate of fetal complications was comparable between the ATRA as compared to the non-ATRA group. Similarly, receipt of consolidation therapy in the study population was not associated with obstetric or fetal complications (Verma et al. 2016). Moreover, CTX rather increases the risk of abortion, prematurity, low birth weight, neonatal neutropenia, and sepsis, than to cause congenital malformations (Culligan et al. 2007).

Potentially, ATRA could be given as single agent therapy with the addition of an anthracycline after delivery. In case presentations, equivalent remission rates of ATRA as compared to CTX/ATRA have been observed (Fadilah et al. 2001; Harrison et al. 1994; Stentoft et al. 1994; Lipovsky et al. 1996). However, in pregnancies with a gestation of at least 20 weeks, there is still a risk of major malformations with ATRA monotherapy (Lammer et al. 1985). Additionally, ATRA monotherapy increases the risk of DS and possible ATRA resistance (Fenaux et al. 1999). Thus, the *PML-RARA* transcript needs to be monitored carefully by quantitative reverse-transcriptase polymerase chain-reaction (RT-qPCR); rise of the *PML-RARA* transcript potentially indicates the need to introduce CTX (Culligan et al. 2007).

As a result, ATRA monotherapy seems to be a valid option during the second or third trimester and low/intermediate-risk APL. However, molecular remission should be monitored carefully by RT-qPCR. Alternatively, in spite of the limited clinical experience, ATRA in combination with an anthracycline, particularly daunorubicin, seem reasonably safe during the second or third trimester of pregnancy.

We recommend a combination of CTX/ATRA for high-risk patients, and where RT-qPCR monitoring for *PML-RARA* is not feasible. Figure 8.3 shows the suggested approach to APL during pregnancy.

In addition, stringent fetal monitoring, with particular emphasis on cardiac function, is recommended for patients receiving ATRA during pregnancy because some cases of reversible fetal arrhythmias have been reported (Culligan et al. 2007; Siu et al. 2002; Terada et al. 1997).

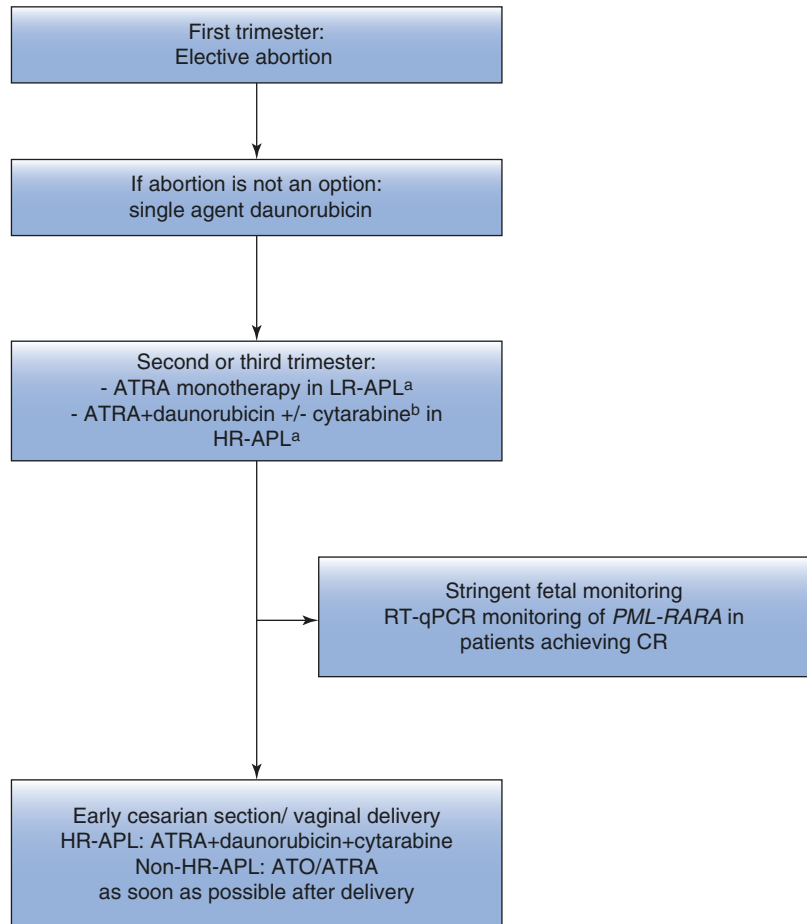
ATO has been shown to be embryotoxic and to induce teratogenicity in animal studies (Holson et al. 2000). Therefore, ATO cannot be recommended throughout pregnancy. Similarly, GO is not justifiable for use in pregnancy (Culligan et al. 2007).

Finally, men and women of childbearing potential should use effective contraception, and breastfeeding must be discontinued during CTX or treatment with ATO.

8.6.5 Treatment of Extramedullary Relapse

Relapse at extramedullary sites was reported to occur in 3–5% of patients after CTX/ATRA, particularly within the CNS (Tallman 2007). Predictive factors for an extramedullary relapse may include the development of an ATRA syndrome (Ko et al. 1999), the predominance of the *PML-RARA* breakpoint cluster region isoform 3 (de Botton et al. 2006) and high-risk APL (de Botton et al. 2006; Breccia et al. 2003; Montesinos et al. 2009b). Montesinos et al. have evaluated the incidence of CNS recurrence on a large group of 739 patients between 1996 and

Fig. 8.3 Suggested algorithm for management of pregnancy in acute promyelocytic leukemia. *APL* acute promyelocytic leukemia, *ATO* arsenic trioxide, *ATRA* all-trans retinoic acid, *HR* high-risk, *LR* low-risk, *PML* promyelocytic leukemia, *RARA* retinoic acid receptor alpha, *RT-qPCR* quantitative reverse-transcriptase polymerase chain-reaction, *WBC* white blood count. ^aAddition of cytarabine in high-risk APL; ^bRisk categorization based on WBC at diagnosis (low-/intermediate-risk: $WBC \leq 10.0 \times 10^9/L$; high-risk: $WBC > 10.0 \times 10^9/L$)



2005 treated on the LPA96 and LPA99 PETHEMA trials (Montesinos et al. 2009b). No CNS prophylaxis was given in either protocol. Overall, CNS relapse was documented in 11 patients and the 5-year CIR within the CNS was 1.7% (Montesinos et al. 2009b). Of note, patients with high-risk had a CIR of 5.5% as compared to 0% and 0.8% in low- or intermediate-risk patients, respectively. Another independent risk factor was CNS hemorrhage during induction therapy (5-year CIR 18.7%, $P = 0.006$) (Montesinos et al. 2009b).

However, the strategy of an up-front CNS prophylaxis in high-risk patients is still a matter of debate. For low-risk patients, in whom the risk of CNS relapse is extremely low, there is a general consensus to avoid CNS prophylaxis (Sanz et al. 2019). Nevertheless, the possibility of CNS disease should be considered in any relapsed patient,

particularly in those with neurological symptoms.

Data on the ability of ATO to cross the blood-brain barrier are derived from single case descriptions are fairly contradictory. Knipp et al. reported on a 42-year-old APL patient who developed a hematological relapse 1 year after AIDA-based therapy (Knipp et al. 2007). Since this patient had previously experienced an ATRA syndrome, he received ATO 10 mg daily for 30 days plus intrathecal therapy (40 mg cytarabine, 40 mg prednisone, and 15 mg MTX three times weekly for a total of nine treatments). In addition, his neuroaxis was irradiated with 30 Gy. Measurement of ATO in the cerebrospinal fluid (CSF) revealed a low CSF concentration of 0.11 $\mu\text{mol/L}$, representing only about 14% of blood levels. The authors concluded that ATO seems to cross the blood-CSF barrier when

administered intravenously, but the concentration in CSF is probably not sufficient for treatment of meningeal leukemia (Knipp et al. 2007). Au et al. reported on a patient who relapsed 9 months after induction and consolidation therapy with ATRA, daunorubicin, and cytarabine (Au et al. 2000). Since reinduction with ATRA and cytarabine (four doses of 3 g/m²) failed, he was treated with ATO at 10 mg/day. Eight months after achievement of a second CR, the patient experienced a second hematological relapse with involvement of the CNS. Despite urgent radiotherapy, the patient died of massive CNS bleeding 2 days later (Au et al. 2000). Hence, treatment with ATO seemed not sufficient to prevent CNS relapse. Contrary, Helwig et al. reported on a patient who was diagnosed with relapsed APL involving the CNS (Helwig et al. 2007). Treatment with ATO led to morphological changes in CNS cellularity consistent with the induction of a DS. Since ATO could be identified in the CNS, the authors concluded that the drug can cross the blood-brain barrier and could be used for treatment of extramedullary APL (Helwig et al. 2007).

Since the existing data are rather limited as well as contradictory, we recommend using triple intrathecal therapy with MTX, corticosteroids, and cytarabine until complete clearance of blasts in the CSF in case of a confirmed CNS relapse/involvement, followed by 6 to 10 more space out intrathecal therapies as consolidation therapy. Since a CNS relapse is almost invariably accompanied by a hematological or molecular relapse in the marrow, systemic therapy should also be given (Sanz et al. 2009).

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