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REVIEW ARTICLE

Acute Myeloid Leukemia

Management of patients with acute promyelocytic leukemia

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Abstract

With the introduction of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) acute promyelocytic leukemia (APL) has become from a detrimental to one of the most curable malignant diseases in humans. In particular, the chemotherapy-free regimen with ATO/ATRA has been proven to be highly effective in de novo APL and has become standard first-line therapy in younger adult, non-high-risk patients. Nevertheless, early death is still a major issue in APL, particularly in older patients, emphasizing the need of rapid diagnostics and supportive care together with immediate access to ATRA-based therapy. Despite the dramatic progress achieved in therapy of APL challenging situations occur, particularly in patients excluded from controlled studies with clinical knowledge mainly based on case reports and registries. Rapid identification and treatment of newly diagnosed patients as well as the management of toxicities and complications remain challenging. We offer up-to-date information and guidance regarding treatment of APL. Based on a literature review of existing scientific evidence we also discuss the approach to high-risk, elderly, pregnant and pediatric patients, treatment in patients with renal failure as well as of therapy-related or relapsed/refractory APL.

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 [1]. Treatment with all-trans retinoic acid (ATRA) has significantly revolutionized therapeutic success in APL, providing the first paradigm of molecularly targeted treatment [2, 3]. However, although complete remissions (CR) were achieved with single-agent ATRA in up to 80–90% of newly diagnosed and relapsed APL patients, remissions in most of them were not sustained [2–7]. 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 [8]. 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 APL, with a CR rate of 96% [9]. 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% ($P = 0.02$) [10]. 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 [11]. 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 [11]. Additional support comes from another publication out of the Medical Research Council with a 4-year EFS rate of 91% after ATO/ATRA as compared to 70% after CTX/ATRA ($P = 0.002$) [12].

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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 [11]. Taken together, the CTX-free regimen with ATO/ATRA has become standard first-line therapy in non-high-risk de novo APL. In countries where ATO is not yet available AIDA-based CTX is still the standard.

Despite the dramatic progress achieved in front-line therapy of APL with ATO/ATRA shown in controlled randomized trials challenging situations occur particularly in patients normally excluded from controlled studies with clinical knowledge mainly based on case reports and registries. Hence, we here discuss specific situations and scenarios in patients with APL for whom treatment decisions need to be made and where clinical management is often challenging. We provide up-to-date information as well as personal experience and guidance regarding successful management of these patients.

Supportive measures and management of complications

Treatment of coagulopathy

APL is typically associated with frequently life-threatening hemorrhagic diathesis, which is attributed to a disseminated intravascular coagulation-like coagulopathy [1, 13, 14]. 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 [15]. The hemorrhagic diathesis, which can result in intracerebral and pulmonary hemorrhages, is one of the main causes of early death (ED) in APL patients [14, 15]. Release and exposure of tissue factor and annexin II by the leukemic blasts are triggering these processes. It is, therefore, also considered that the absolute leukemic mass, as reflected by absolute leukocyte count, correlates with the severity of bleeding complications in these patients [15].

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 [16]. Therefore, current guidelines advise to start ATRA as soon as the diagnosis of APL is suspected to treat and prevent hemorrhagic complications [17]. 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 antifibrinolytic 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 [14]. 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 [18, 19], theoretically these agents may enhance the thrombotic risk [15, 16]. Thus, 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 [17].

Apart from early administration of ATRA + /- CTX in suspected cases of APL, 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 30×10^9/l, respectively [17]. 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. In fact, in the APL0406 trial [10] there was no case of early hemorrhagic death in the ATO/ATRA-arm for patients with low-risk (pretreatment WBC $\leq 10 \times 10^9$/l) disease. 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.

Therapy of differentiation syndrome

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 [20]. 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 [21].

If DS is suspected, 10 mg dexamethasone twice daily intravenously 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 [17].

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 APL 93 trial, in which prophylactic dexamethasone was not used [14, 22]. Within the APL0406 trial, prednisone was given prophylactically at a dose of 0.5 mg/kilogram/day from day 1 until the end of induction therapy [10]. 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 [10]. Based on these results, we recommend prednisone prophylaxis as done in the APL0406 trial.

Treatment of leukocytosis during induction

Leukocytosis commonly occurs, either at initial presentation or during therapy in patients treated with ATRA and/or ATO induction. Thus, in low-risk APL, hydroxyurea 500 mg once/daily for WBC between 10 and 20×10^9/l, 500 mg twice/daily for WBC between 21 and 50×10^9/l, and 1.0 g twice daily above 50×10^9/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 [10]. In addition, APL cells are sensitive to therapy with anthracyclines, which should, therefore, 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 [23]. 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 [12].

In contrast, leukapheresis has no up-front role 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 [24].

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 [25, 26]. 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 ≥ 501 milliseconds) in one patient. Thus, close monitoring of the electrocardiogram and electrolytes is necessary during treatment with ATO. In particular, 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 we highly suggest resuming ATO 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 given at full dose [10].

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 [27]. 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 [27]. However, the common signs of chronic arseniasis, such as cardiovascular events, chronic renal insufficiency, diabetes, or neurological dysfunction, were not observed [27]. In some cases peripheral neuropathy has been reported during and after treatment with ATO [28, 29]. Symptoms are usually mild and reversible following discontinuation of treatment but may be severe and irreversible in patients with coexistence of thiamine deficiency [28].

Based on this limited data, no firm conclusions can be drawn regarding the occurrence of comorbidities and organ toxicities. However, we suggest routinely 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.

Therapy in patients with 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 [30, 31]. Due to its success in de novo non-high-risk APL [10], 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 [9, 30–34].

Recently, Abaza et al. [35] published outcome data on 187 APL patients, including 54 with high-risk APL. 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 [9, 34]. Similar results were reported by Burnett et al. [12] on the phase 3 AML17 trial comparing ATO/ATRA with CTX/ATRA in newly diagnosed patients with APL. High-risk patients treated with ATO/ATRA received an 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 [12]. Currently, the European randomized intergroup study "APOLLO" investigates idarubicin 12 mg/m^2 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 [18] approach (ClinicalTrails.gov identifier: NCT02688140).

We recommend starting immediately with idarubicin + ATRA in high-risk patients. 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 [30]. This approach is also supported by published data combining intensive CTX according to the 7 + 3 scheme and ATRA [36].

In addition, a positive impact of adding ATO to consolidation regimens was reported for all risk groups of APL in the C9710 trial [37]. The efficacy of ATO as consolidation therapy was recently confirmed by Lou et al. [38], who reported that treatment with ATO as postremission therapy significantly improved long-term outcome as compared to standard CTX.

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

Maintenance therapy in patients with high-risk APL

The clinical benefit of maintenance therapy particularly in patients with negative measurable residual disease (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 [39]. 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 [3, 40–42]. 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 [43–45]. Moreover, it's currently unclear, if maintenance therapy further enhances the risk of induction of 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) [46]. 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 [46].

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 [47]. 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 [48, 49]. Thus, a home-based treatment without need of daily hospital visits and monitoring for QT prolongation or cardiac arrhythmias seems to be feasible.

Recently, Au et al. [50] have published 10 years follow-up data on outcome after oral ATO-based maintenance therapy. Seventy-six APL patients in first CR after induction and consolidation by 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 [50].

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 [10]. 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.

Treatment of elderly patients

Although it is generally noted that APL seems to be rather uncommon in elderly patients [17] 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 [51]. 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 with 60% highest 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 [51]. Although speculative, we assume that during the pre-admission phase, many elderly patients are probably lost due to cerebral hemorrhage or other severe bleeding events, which are often facilitated by the concomitant use of oral anticoagulants commonly used in this age-group due to comorbidities.

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 [52]. Patients who were MRD-negative at the end of consolidation received oral 6-MP (50 mg/m^2/day), intramuscular MTX (15 mg/m^2/week), and ATRA (45 mg/m^2/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 [52]. However, CR-rate was lower in patients older than 70 years as compared to patients aged 60–70 years (74% vs. 89%) [52]. These results had recently been confirmed by Martinez-Cuadrón et al. [46] comparing the long-term outcome of older patients (median age, 67 years) with de novo APL treated within the LPA2005 vs. LPA96&99 trials. 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 [46].

However, contrary results had been published recently by Lengfelder et al. [53] who reported on 91 newly diagnosed APL patients (median age, 67 years) registered by the German AML Cooperative Group since 1994. 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 patients since elderly patients have a higher vulnerability to treatment toxicity [53]. Sanz et al. [52] noted that 6 of 25 (24%) patients ≥ 70 years died in remission, while Ades et al. [54] reported that 19% of patients ≥ 60 years died due to complications of myelosuppression during consolidation with daunorubicin/cytarabine. 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 [52, 53]. Sanz et al. [52] 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. In contrast, Lengfelder et al. reported on 31% ($n = 28/91$) of patients with high-risk APL [53].

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 [10]. 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. [55] 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. 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 (Table 1). 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, although reduced intensities of CTX in older patients were reported in different trials [54, 56, 57], NRMs during postremission therapy were high, up to 10% to

Table 1 Overview of published data of treatment in elderly, newly diagnosed patients with acute promyelocytic leukemia

No. of patients (No. according to age)	Median age (years, range)	Study period	Treatment	Response to induction	Outcome	Reference
134 (≤70 yrs: 115>70 yrs: 19)	66 (60–75)	1993–2001	Induction: AIDA Consolidation: IDA + AraC- > mito + eto- > IDA + AraC + 6-thioguanine vs. 1 × IDA + AraC Maintenance: 2 yrs ATRA (for 15 days every 3 months) for pts in molecular CR after 1 × IDA + AraC	CR: 86% CR according to age: ≤70 yrs: 90% >70 yrs 63% ED: 12% Resistant: 2%	6-yrs OS: 56% DFS: 59% Death during postremission: 10%	Mandelli et al. [56]
104 (60–70 yrs: 70>70 yrs: 34)	68 (60–83)	1996–2003	Induction: AIDA Consolidation: IDA- > mito-IDA Maintenance: 2 years 6-MP/MTX/ATRA For pts in molecular CR	CR: 84% CR according to age: 60–70 yrs: 89%>70 yrs: 74% ED: 15% Resistant: 1%	6-yrs DFS: 79% CIR: 8.5% Death during postremission: 9.2% (24% in pts ≥ 70 yrs)	Sanz et al. [31]
129 (60–70 yrs: 95>70 yrs: 34)	66 (62–70)	1993–1998	Induction: ATRA/DNR/AraC Consolidation: ATRA/DNR/AraC- > DNR + AraC (last cycle only in pts ≤ 65 yrs) Maintenance: 2 years ATRA vs. no maintenance; 6-MP/MTX/ATRA vs. no maintenance	CR: 86% CR according to age: > 70 yrs: 85% ED: 14%	4-yrs OS: 57.8% EFS: 53% CIR: 15.6% Death during postremission: 19%	Ades et al. [54]
13	78 (71–87)	1999–2006	Induction: ATRA/DNR/AraC Consolidation: 2 × ATRA/DNR/AraC or 2 × ATRA/AMSA/AraC Maintenance: 9 months: ATRA or 6-MP/MTX/ATRA ($n = 1$)	CR: 92% Resistant: 8%	2-yrs OS: 76% RFS: 59% Death during postremission: 17%	Disperati et al. [57]
34	70 (61–84)	2005–2007	Induction: AIDA Consolidation: IDA + AraC - > mito + eto - > IDA + AraC + 6-thioguanine; GO ($n = 3$) Maintenance: for pts in molecular CR: 2 yrs 6-MP + MTX vs. ATRA alone vs. alternating ATRA or 6-MP/MTX vs. no maintenance	CR: 68% ED: 32%	OS: 38 months Death during postremission: 0 Relapses: 35%, with 75% achieving 2nd CR after ATO or ATO/ATRA	Ferrara et al. [138]
33 (60–69 yrs: 28; ≥ 70 yrs: 5)	65 (60–79)	1996–2002	Induction: ATO Consolidation: ATO Maintenance: ATO up to 4 yrs	CR: 88% ED: 12%	10-yrs OS: 69.3% DFS: 64.8% CIR: 10.3% Death during postremission: 6.9%	Zhang et al. [55]
56 (60–60 yrs: 38≥70 yrs: 18)	67 (60–87)	1994–2011	Induction: ATRA/ TAD;2nd cycle with HAM ± ATRA possible Consolidation: TAD Maintenance: 3-years, monthly: AraC s.c. + either DNR (course 1 + 5) or 6-TG (course 2 & 4) or cyclo (course 3)	CR: 82% CR according to age: 60–69 yrs: 89%≥70 yrs: 67% ED: 18% ED according to age: 60–69 yrs: 11%≥70 yrs: 33%	7-yrs OS: 45% EFS: 40% CIR: 24% According to age:60–69 yrs: OS: 54% EFS: 46% CIR: 26% ≥ 70 yrs:OS: 25% EFS: 28% CIR: 19%	Lengfelder et al. [53]

Table 1 (continued)

No. of patients (No. according to age)	Median age (years, range)	Study period	Treatment	Response to induction	Outcome	Reference
13	74.8 (70–81)	1991–2008	Induction: AIDA ($n = 9$) ATRA mono ($n = 2$) ATRA + mito + AraC ($n = 2$) Consolidation: CTX ($n = 7$) CTX/ATRA ($n = 4$) Maintenance: ATRA, $n = 7$ ATRA + INF, $n = 1$ 6-MP/MTX/ATRA, $n = 1$ 6-MP/MTX/INF, $n = 1$	CR: 100%	5-yrs OS: 64.5% EFS: 56.1% Relapse: $n = 5$ Death during postremission: 0	Finsinger et al. [139]
56 (60–60 yrs: 38≥70 yrs: 18)	47 (16–77)	2009–2013	Induction: AIDA vs. ATO/ATRA (± GO in high-risk pts) Consolidation: AIDA- > ATRA/mito- > AIDA vs. 4xATO/ATRA Maintenance: no	AIDA vs. ATO/ATRA: CR: 89% vs. 94% ED: 6% vs. 4% Pts ≥ 60 yrs: CR and ED not reported	AIDA vs. ATO/ATRA: 4-yrs OS: 89% vs. 93% EFS: 70% vs. 91% CIR: 18% vs. 1% OS (pts ≥ 60 yrs): 74% vs. 80%	Burnett et al. [12]
268 (60–69 yrs: 169 70–79 yrs: 91≥80 yrs: 8)	67 (60–84)	1996–2012	Induction: AIDA Consolidation: IDA/mito/IDA vs. AIDA/mito + ATRA/AIDA Maintenance: 2-yrs 6-MP/MTX/ATRA	CR: 81% ED: 19%	LPA96&99 vs. LPA2005: 5-yrs OS: 60% vs. 74% DFS: 69 vs. 87% NRM: 18 vs. 5% CIR: 12 vs. 7% 5-yrs OS according to age: 60–69 yrs:66% vs. 77%⩾70 yrs: 49 vs. 68%	Martinez-Cuadrón et al. [46]

AIDA all-trans retinoic acid + idarubicin, *ATO* arsenic trioxide, *ATRA* all-trans retinoic acid, *CIR* cumulative incidence of relapse, *CR* complete remission, *cyclo* cyclophosphamide, *DFS* disease-free survival, *DNR* daunorubicin, *ED* early death, *EFS* event-free survival, *eto* etoposide, *GO* gemtuzumab ozogamicin, *HAM* AraC 1 g/m^2 infusion every 12 h, days 1–3, mitoxantrone, *IDA* idarubicin, *INF* interferon-alpha, *6-MP* 6-mercaptopurin, *mito* mitoxantrone, *MTX* methotrexat, *No* number, *NRM* non-relapse-mortality, *OS* overall survival, *pts* patients, *s.c.*, subcutaneously, *TAD* 6-thioguanine, AraC 100 mg/m^2 daunorubicin, *6-TG* 6-thioguanine, *vs.* versus, *yrs* years

18.6%, mainly due to infection, whereas it was only 6.9% after monotherapy with ATO due to noninfectious diseases [55]. 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 [55].

In comparison, a subgroup analyses of the randomized phase 3 AML17 trial on older patients showed no significant difference of 4-year OS after treatment with ATO/ATRA (74%; $n = 25$) as compared to AIDA-based regimen (80%; $n = 24$). However, further subgroup analyses on important survival endpoints, such as EFS, RFS, and CIR, were not presented within this age-group [12]. Within the total study cohort, EFS, RFS as well as CIR were significantly better after ATO/ATRA as compared to the AIDA-based regimen [12].

Table 1 gives an overview on published data in older APL patients.

Taken together, it seems reasonable to offer ATO/ATRA as first-line treatment to older patients in case of non-high-risk disease while rare cases with high-risk disease need to be treated on an individual basis with ATRA as backbone also taking into account performance status and comorbidities.

Treatment in patients with renal failure

Regarding therapy in patients with renal failure data are limited to case reports only. Tsuchiya et al. [58] reported on successful treatment of a 64-year old patient with low-risk APL requiring hemodialysis due to autosomal dominant polycystic kidney disease. ATRA 40 mg/m² was given as induction and CR was achieved after 1 month. Consolidation therapy consisted of 100 mg/m² cytarabine on days 1–5 and 4.7 mg/m² mitomycin C on days 1–3 and molecular remission was achieved thereafter. Two further consolidation cycles were administered (cycle 2, 100 mg/m² cytarabine on days 1–5, and 33 mg/m² daunorubicin on days 1–3; cycle 3, cytarabine 100 mg/m² on days 1–5 and 7.9 mg/m² idarubicin on days 1–3). Maintenance therapy

Table 2 Fetal and maternal outcome of pregnant patients with acute promyelocytic patients

No. of pregnant women	Treatment	Maternal Outcome	Fetal Outcome	Reference no.
71 (systematic review)1st trim: 16 2nd trim: 20 3rd trim: 28 Unk: 7	ATRA/anthracycline/AraC: $n = 9$ ATRA/anthracycline: $n = 30$ ATRA: $n = 16$ Anthracycline/AraC: $n = 10$ Others: $n = 6$	CR: 93% (53/58) Obstetric complications during 1st as compared to 2nd/3rd trim: 86.7% vs. 15.9% Premature Cesarean section or induction of labor: 41% (27/66) Relapses: $n = 4$ after a median follow-up of 10.5 months; salvage with CTX ± ATRA, 2 deaths due to APL, 1 death due in 2nd CR	Outcome reported of $n = 54$ Preterm: $n = 25$ spontaneous or therapeutic abortion or intrauterine death: $n = 18$ Fetal complications during 1st as compared to 2nd/3rd trim: 92.3% vs. 37.5% Complications included: respiratory distress syndrome: $n = 6$ oligohydramnios and intrauterine growth retardation: $n = 4$ arrhythmias or cardiac issues: $n = 3$ mild intraventricular brain hemorrhage: $n =$	Verma et al. [72]
14 1st trim: 3 2nd trim: 2 3rd trim: 7 After delivery: 2	AIDA: 12	CR: 92% (11/12) ED: 2 (due to hemorrhage)	1st trim: 5 abortions 2nd and 3rd trim: normal development in $n = 8$,1 dead fetus (26th week of gestation)	Sanz et al. [67]
1 (3rd trim)	ATRA mono	CR: 100%	Cesarean section after 30 weeks: $n = 1$	Culligan et al. [85]
1 (2nd trim)	ATRA/CTX	CR: 100%	Normal, but premature (35th week of gestation)	Giagounidis et al. [84]
1 (2nd trim)	ATRA mono (30 days)	CR: 100%	Cesarean section (30 weeks of gestation)Cardiac arrhythmia and sustained cardiac arrest	Harrison et al. [87]
1 (3rd trim)	ATRA mono	CR: 100%Massive bleeding during delivery (extensive vaginal and perineal rupture)	Normal development	Stentoft et al. [88]
1 (3rd trim)	ATRA mono for 4 weeks until delivery2 weeks postpartum: consolidation cycles with daunorubicin/AraC	CR: 100%	Induced labor, vaginal delivery, normal development	Lipovsky et al. [89]
1 (2nd trim)	Four 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. [90]
1 (3rd 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. [91]

Table 2 (continued)

No. of pregnant women	Treatment	Maternal Outcome	Fetal Outcome	Reference no.
3 1st trim: 1 3rd trim: 2	First patient (1st trim): AIDA after therapeutic abortion Second patient (3rd trim): AIDA 1 week after cesarean section Third patient (3rd trim): ATRA for 2 weeks before delivery	CR: 67% ED: 33% due to ATRA syndrome 1 week after delivery	Normal development	Consoli et al. [83]

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

consisted of 40 mg/m² ATRA intermittently. The patient remained in complete molecular remission after 42 months of follow-up.

In the past, ATRA was thought to be contraindicated for patients with renal failure due to the possible induction of severe hypercalciemia [59]. However, Okazuka et al. [60] reported on the successful induction therapy with ATRA at a daily dosage of 20 mg/m² without any AEs. In addition, Rajpurkar et al. [61] stated that ATRA dose modification might not be necessary since pharmacokinetic analysis in their single case experience did not result in improved clearance compared with days off dialysis.

In patients with renal impairment the active metabolite of cytarabine accumulates and increases the half-life of cytarabine to 12 times longer than in patients without severe renal insufficiency [62]. Thus, the dose of cytarabine has to be reduced to two-thirds or half of the usually dosage. In dialysis-dependent patients, however, cytarabine levels are not increased, since it can be dialyzed [62]. Additionally, anthracyclines are excreted in the urine requiring a dose modification. Since data are scarce, we suggest the reduction of the dose empirically to two-thirds of the usually used dosage.

Treatment with ATO during hemodialysis

ATO is metabolized mainly via the liver and data on the use of ATO in APL patients requiring dialysis are scarce. Perreault et al. [63] reported on an 81-year old patient who relapsed after AIDA-based regimen. Due to preexisting cardiac and renal comorbidities (including chronic hemodialysis), ATO was given at a fixed dose of 10 mg, initially twice weekly and increased to three times weekly after 11 doses of ATO due to refractory disease. After a total of 47 doses, cytogenetic and morphological CR was achieved. Eventually, the patient died due to hemorrhagic stroke in morphological CR. Firkin et al. reported on four patients with severe chronic renal failure (two patients were hemodialysis-dependent), who had successfully been treated with fixed ATO doses of 5–10 mg/day or 5–10 mg three times/weekly [64]. All patients achieved molecular CR after one or two treatment courses with a RFS of 5–155 months. Further, successful use of ATO at a dose of 0.15 mg/kg twice or three times/weekly or even every other day/weekly was reported [65, 66].

Taken together, no standard therapy in patients on hemodialysis has been established. Nevertheless, according to the limited number of case reports presented, we suggest to use ATO ± ATRA initially at a lower dosage as outlined above, e.g., 50% of dose or 0.15 mg/kg twice or three times weekly.

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 [67]. 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 [67]. Besides supportive therapy, the initiation of effective APL treatment to stop coagulopathy is of utmost importance [17]. Table 2 provides an overview of fetal and maternal outcome after treatment of pregnant APL patients.

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 [17]. 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 [68–71]. 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 [72]. 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 complications as compared to the subsequent trimesters [72]. 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 [68–71]. Cytarabine and/or anthracyclines are known to increase the risk of spontaneous abortions or cause major malformations by up to 20% [73–77].

Thus, the option of therapeutic abortion has to be discussed with the patient, in particular during the first trimester. In those cases, where 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 [78, 79], we recommend using daunorubicin 60 mg/m² for a maximum of 3 consecutive days. The addition of cytarabine 100–200 mg/m² days 1–7 should be considered during induction and consolidation [80, 81], particularly in patients with high-risk APL.

It should be well taken, that CTX alone, however, increases the risk of hemorrhage due to the release of procoagulants and plasminogen activators from malignant cells [14].

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.

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 [67, 82–84]. 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 [72]. 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 [72]. Moreover, CTX rather increases the risk of abortion, prematurity, low birth weight, neonatal neutropenia, and sepsis, than to cause congenital malformations [85].

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 [86–89]. However, in pregnancies with a gestation of at least 20 weeks, there is still a risk of major malformations with ATRA monotherapy [68]. Additionally, ATRA monotherapy increases the risk of DS and possible ATRA resistance [39]. This should be carefully monitored by quantitative reverse-transcriptase polymerase chain-reaction (RT-qPCR); rise of the *PML-RARA* transcript potentially indicates the need to introduce CTX [85].

Thus, ATRA monotherapy seems to be a valid option during 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

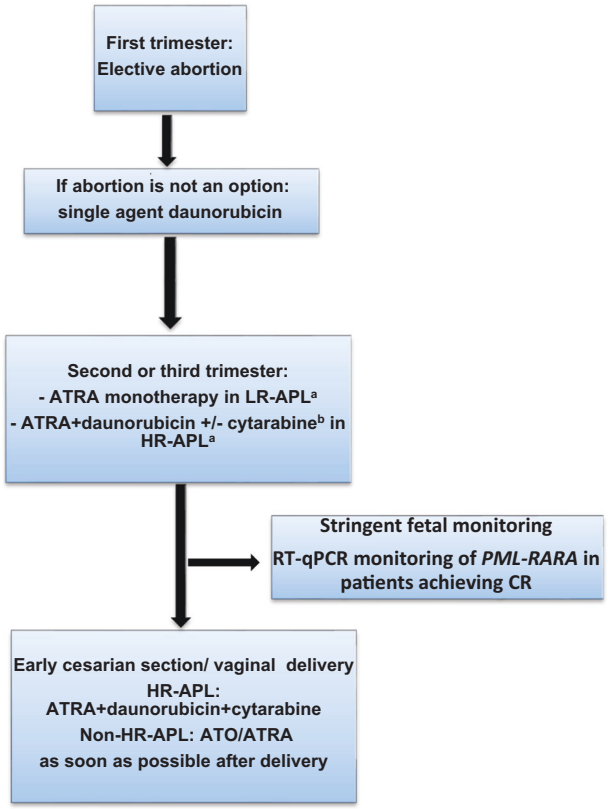

Fig. 1 Suggested algorithm for management of pregnancy in acute promyelocytic leukemia. APL acute promyelocytic leukemia, ATO arsenic trioxide, ATRA all-trans retinoic acid, HR high-risk, LR low-risk, PML promyelocytic leukemia, RARA retinoic acid receptor alpha, RT-qPCR quantitative reverse-transcriptase polymerase chain-reaction, WBC white blood count. [a]Addition of cytarabine in high-risk APL; [b]Risk categorization based on WBC at diagnosis (low-/intermediate-risk: WBC ≤ 10.0 x 10^9/l; high-risk: WBC > 10.0 x 10^9/l)

patients, and where RT-qPCR monitoring for *PML-RARA* is not feasible. Figure 1 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 [85, 90, 91].

ATO has been shown to be embryotoxic and to induce teratogenicity in animal studies [92]. Therefore, ATO cannot be recommended throughout pregnancy. Similarly, GO, is not justifiable for use in pregnancy [85].

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

Treatment in pediatric APL

APL in pediatric patients seems to be rare and may vary according to geographic areas. In the United States, as in central and northern Europe, the percentage of APL patients accounts for 4–8% of pediatric AML patients, whereas about 20% was reported from Italy and Central and South Africa [93–96].

Childhood APL has customarily been treated on adult protocols. Data from several trials have shown that the overall outcome in pediatric APL appears similar to that reported for the adult population [95–97]. Yet, some clinical and therapeutic aspects differ between adult and pediatric APL. In particular, childhood APL is more frequently associated with leukocytosis (35% to 48%) [93, 94], as compared to the disease in adults. In addition, treatment with ATRA is frequently associated with headache and idiopathic intracranial hypertension, commonly called pseudotumor cerebri (PTC) [39], particularly in children [95, 96]. In the European APL 93 trial with an ATRA dose of 45 mg/m^2 severe headache episodes were more frequent in the pediatric population than in adults (16% vs. 1–2%) [39, 96]. However, a dose of 25 mg/m² proved to be equally effective with a lower incidence of AEs [93, 94] and is, therefore, recommended as standard for children [96, 98].

Despite excellent outcomes, treatment of pediatric APL with anthracyclines may cause severe cardiotoxicity, particularly if high doses of anthracyclines are used [93, 94, 99–101]. Late subclinical cardiotoxicity was observed in 52% of the adult survivors of APL treated on the GIMEMA AIDA-0493 and -2000 protocols [102]. Due to the obvious concerns of irreversible heart failure in children who receive high cumulative doses of daunorubicin, the CALGB C9710 study utilized a cumulative dose of daunorubicin of 500 mg/m^2 for those > 15 years of age and 400 mg/m^2 in children 3–14 years of age [37]. To reduce the risk of developing clinically significant cardiotoxicity and heart failure, which is approximately 5% at 15 years after anthracycline therapy for childhood cancer, the AML BFM study group limited the cumulative anthracycline dose to 350 mg/m^2 in most APL patients, obtaining results comparable to those reported for studies with higher doses [103].

Therapy with ATO in pediatric patients

Regarding the use of ATO for the treatment of pediatric APL, data from small case series indicate, that outcome after ATO in pediatric APL appears similar to that reported for the adult population with a CR rate of 91% and 89.5% and an estimated 5-year OS and EFS of 91% and 81% and 84% and 73%, respectively [104–106]. ATO-related toxicity was minimal and transient during induction, and neutropenia was the most common side-effect during the 3-year postremission ATO therapy. Recently, the Children's Oncology Group AAML0631 trial for newly diagnosed pediatric APL evaluated consolidation therapy with ATO/

ATRA. This regimen was well tolerated in pediatric patients with APL and allowed a significant reduction in cumulative anthracycline doses while maintaining excellent survival and a low relapse risk (4% at 3 years) for both standard and high-risk patients with APL [107]. In addition, Creutzig et al. [108] reported in a small pilot study on their experience of 11 pediatric patients with low-risk APL who were treated with ATO/ATRA. While all of them achieved molecular remission, two experienced severe, but reversible AEs (one patient with osteonecroses at both femurs, seizures, as well as posterior reversible encephalopathy syndrome, the other patient had an abducens paresis).

Taken together, the front-line use of ATO/ATRA is extremely encouraging and will probably become the standard regimen also in the pediatric age.

Treatment in patients with therapy-related APL

Reports of patients with therapy-related APL (t-APL) as a result of previous exposure to CTX and/or radiation have increased in recent years, particularly for those who received treatment with topoisomerase II inhibitors or alkylating agents [109–114].

Prior publications have suggested that characteristics and outcomes of t-APL when treated appropriately were similar to those of de novo APL patients [113, 115]. Very recently, we have evaluated the outcome of patients with t-APL according to treatment strategy (single-agent ATRA in older, frail patients, $n = 7$; ATO/ATRA, $n = 24$; CTX/ATRA, $n = 53$; CTX/ATO/ATRA, $n = 19$) in a large international multicenter analysis [116]. Our analysis corroborated the results in non-high-risk de novo APL: EFS was significantly higher after ATO-based therapy (95%) as compared to CTX/ATRA (78%; $P = 0.042$), if deaths due to recurrence of the prior malignancy were censored. None of the patients treated with ATO-based regimen relapsed nor developed a therapy-related myeloid neoplasm. In comparison, three patients treated with CTX/ATRA relapsed and two patients developed t-AML with a complex karyotype. Notably, all of the t-APL relapses could be successfully salvaged with ATO/ATRA ± CTX and went on to autologous or allogeneic transplant [116].

Therefore, we recommend ATO/ATRA as front-line therapy in patients with low-/ intermediate-risk t-APL.

Treatment of molecular resistant or hematological/molecular relapsed patients

Derived from the pre-ATO-era, roughly 10–20% of APL patients eventually relapsed after initial CR, particularly those with high-risk disease [117, 118]. However, recently published data on a randomized phase 3 trial on 276 patients have shown a very low CIR of 1.9% after treatment with ATO/ATRA in low-/intermediate-risk APL as compared to 13.9% after treatment with CTX/ATRA [11]. In addition, none of the patients treated with ATO/ATRA were *PML-RARA* positive by RT-qPCR after the third consolidation as compared to two patients treated with CTX/ATRA, who were considered molecular resistant [11]. The common practice is to treat resistant or relapsed APL patients until molecular CR is achieved and to consolidate with autologous (auto-SCT) or allogeneic hematopoietic stem cell transplantation (allo-SCT) [11, 119–123]. According to recently published data, the 5-year DFS-rates after transplantation in second CR seemed to be comparable between auto- and allo-SCT (51–63% vs. 50–59%) [119, 122]. However, data on 294 patients with APL in second CR receiving allo-SCT ($n = 232$) or auto-SCT ($n = 62$) reported to the Center for International Blood and Marrow Transplantation Research from 1995 to 2006 suggested a significantly worse DFS and OS after allo-SCT in multivariate analysis with a Hazard ratio of 1.88 and 2.66, respectively [119]. The survival advantage for autografting was mainly attributable to an increased treatment-related mortality of 30% after allo-SCT as compared to only 2% after auto-SCT. Astonishingly, positive MRD status did not influence outcome in either group [119]. In addition, Ganzel et al. [124] have compared outcome of patients in second CR after ATO-based therapy alone ($n = 67$) as compared to auto-SCT ($n = 140$), with or without ATO. Again, the 5-years OS rate was significantly higher after auto-SCT (78%) as compared to therapy with ATO (42%; $P < 0.001$) alone, which is in-line with data from the European LeukemiaNet registry [125].

Taken together, the suggested approach in molecular resistant/relapsed patients after CTX/ATRA is an ATO/ATRA-based salvage followed by auto-SCT in case of MRD negativity. In those patients, where SCT is not an option, prolonged administration of ATO/ATRA given as maintenance therapy could be considered. Remission duration seems to be longer when combinations of ATO with either ATRA, CTX or both were used compared with CTX or ATO alone [126, 127].

In the unlikely event of molecular resistance/relapse after ATO-based therapy an AIDA-based salvage followed by cytarabine-based consolidation should be considered. Auto-SCT should be performed once MRD negativity is achieved, whereas allo-SCT should be strongly considered for MRD-positive patients after either salvage regimen.

Fig. 2 shows the suggested approach to patients with resistant/relapsed disease.

In elderly patients or those, who are not considered candidates for salvage therapy, monotherapy with GO might be an option [128].

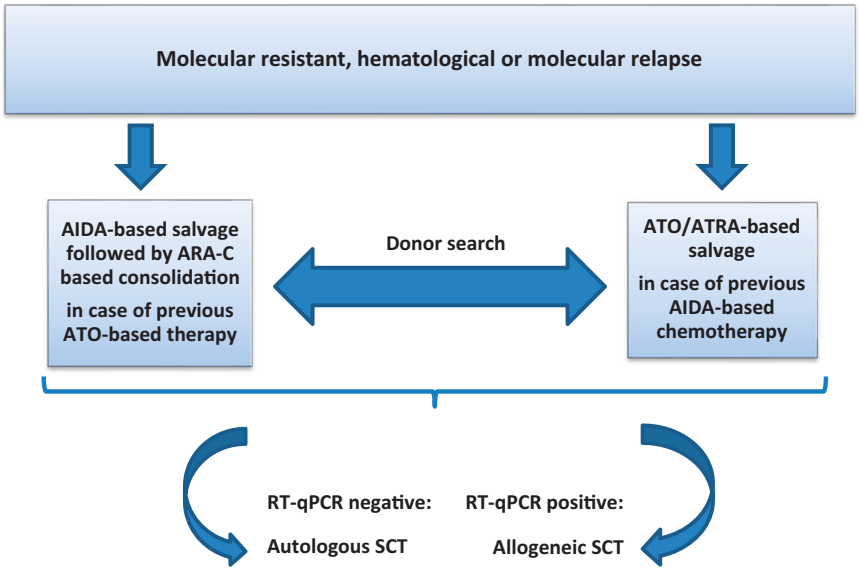

Fig. 2 Suggested algorithm in molecular resistant or relapsed patients. AIDA ATRA+ idarubicin, APL acute promyelocytic leukemia, ARA C cytarabine, ATO arsenic trioxide, ATRA all-trans retinoic acid, RT-qPCR quantitative reverse-transcriptase polymerase chain-reaction, SCT stem cell transplantation

Treatment of extramedullary relapse

Relapse at extramedullary sites was reported to occur in 3–5% of patients after CTX/ATRA, particularly within the CNS [129]. Predictive factors for an extramedullary relapse may include the development of an ATRA syndrome [130], the predominance of the *PML-RARA* breakpoint cluster region isoform 3 [131] and high-risk APL [131–133]. Montesinos et al. [133] have evaluated the incidence of CNS recurrence on a large group of 739 patients between 1996 and 2005 treated on the LPA96 and LPA99 PETHEMA trials. 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% [133]. 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%, $P = 0.006$) [133].

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 [17]. Nevertheless, the possibility of CNS disease should be considered in any relapsed patient, particularly in those with neurological symptoms.

Regarding the possibility of ATO to cross the blood–brain-barrier currently published data, derived from single case descriptions, are fairly contradictory. Knipp et al. [134] reported on a 42-year-old APL patient who developed a hematological relapse 1 year after AIDA-based therapy. 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 Gray. Measurement of ATO in the cerebrospinal fluid (CSF) revealed a low CSF concentration of 0.11 micromol/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 [134].

In addition, Au et al. [135] reported on a patient who relapsed nine months after induction and consolidation therapy with ATRA, daunorubicin and cytarabine. Since reinduction with ATRA and cytarabine (four doses of 3 g/m^2) 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 [135]. Hence, treatment with ATO seemed not sufficient to prevent CNS relapse.

In contrast, Helwig et al. [136] reported on a patient who was diagnosed with relapsed APL involving the CNS. 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 [136].

Hitherto existing data being 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 [17]. Since a CNS relapse is almost invariably accompanied by a

hematological or molecular relapse in the marrow, systemic therapy should also be given [17].

Conclusion

ED, rather than resistant disease is still the major cause of treatment failure. Even with the approval of ATO/ATRA for patients with low-/intermediate-risk APL, we continuously need "real-life" data from large registries of APL patients treated with this CTX-free approach. Auto-SCT seems to be quite successful in second CR in MRD-negative patients, whereas allo-SCT should be considered in MRD-positive patients. Future directions for APL therapy should include developing strategies that can prevent relapse, particularly for high-risk patients. An oral arsenic formula might further improve the treatment strategy in APL patients [137].

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Author contributions SK, RFS, and UP were responsible for the concept of this review, contributed to the literature search data collection, analyzed and interpreted data, and wrote the manuscript.

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