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Contemporary Treatment of APL

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Abstract

Acute promyelocytic leukemia (APL) is characterized by coagulopathy, leukopenic presentation and sensitivity to anthracyclines, all-trans retinoic acid (ATRA) and arsenic trioxide (ATO). For the last 25 years, APL has been treated with a combination of ATRA and chemotherapy for induction followed by consolidation and maintenance therapy. This general treatment approach has resulted in cure rates of 80–90%. ATO, originally approved in relapsed APL, has been incorporated into contemporary upfront treatment regimens with excellent response rates. Recent studies show that most patients with APL can be cured with ATRA and ATO alone, eliminating cytotoxic chemotherapy and resulting in superior outcomes compared to standard treatment. We will herein review historical treatment of APL, treatment considerations in specific patient populations, and therapeutic updates.

Keywords

acute promyelocytic leukemia; arsenic trioxide; all-trans retinoic acid; early death rate

Introduction

Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia (AML) characterized by leukopenia, coagulopathy and high cure rate. APL is a rare disease with approximately 1000 cases diagnosed yearly in the United States [1]. Patients typically present with pancytopenia and complications from coagulopathy [1, 2]. Over 95% of cases are characterized by a balanced translocation of the PML gene on chromosome 15 and the RARA gene on chromosome 17, t(15;17). This results in a PML/RARA fusion protein that inhibits transcription of genes necessary for differentiation. APL cells are sensitive to the differentiating effects of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) [3]. Differentiation of leukemic promyelocytes leads to rapid resolution of coagulopathy, the major cause of early death in APL patients. Studies with single agent ATRA began in the 1980s [4–10], and since that time, ATRA and ATO in varying combinations with chemotherapeutic agents have resulted in cure rates of 80–90% [11]. Based on recent phase

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III data presented by the Italian Group for Haematological Diseases in Adults (GIMEMA), there is now evidence to suggest that chemotherapy can be eliminated completely for low and intermediate risk patients [12]. In this article, we will review the historical data informing current APL treatment and discuss clinical considerations in specific patient populations and recent therapeutic updates.

Historical Overview

With efficacy first reported in the 1980s by investigators from the People's Republic of China, single agent ATRA has been found to induce high complete remission (CR) rates in APL [4–10]. In the 1990s, European and American investigators added ATRA to chemotherapy further improving survival rates [13–16]. The focus then shifted to risk-adapted strategies for APL treatment, partitioning patients into low, intermediate and high risk groups based on white blood cell (WBC) count and platelet count [17–20]. Specifically, WBC over 10,000/ μ L was found to correlate with increased induction death and higher relapse rates [13–16].

ATO was also found to be highly active in APL. ATO breaks down the PML-RAR- α fusion transcript, allowing for transcription of genes necessary for differentiation of promyelocytic leukemia cells and apoptosis [21]. ATO was initially approved for use in the relapsed setting [22, 23]. Studies then transitioned to its use in the upfront setting in combination with chemotherapy and ATRA resulting in impressive outcomes [24–28]. These studies led to the pivotal phase III randomized trial (APL0406) in which ATRA/ATO was shown to be non-inferior to ATRA/chemotherapy for low/intermediate risk patients [12]. Tables 1 and 2 summarize the regimens and outcomes data from significant APL trials conducted in the last 20 years.

Treatment considerations in standard risk APL

Eliminating chemotherapy from treatment

Treatment for low and intermediate risk APL, referred to here as standard risk APL has been redefined based on results from the APL0406 trial. Shen initially reported the benefits of ATRA in addition to ATO in 2004. 61 newly diagnosed patients with APL were randomized to ATRA vs. ATO vs. ATRA/ATO, and CR rates of over 90% were achieved in all arms; however, the combination arm had an improved relapse free survival (RFS) and shorter time to hematologic remission [28]. Estey confirmed a benefit for ATRA plus ATO, achieving a CR rate of 95% in low-risk patients and 79% in high-risk patients [24, 27]. The North American Leukemia Intergroup Study C9710 also evaluated adding ATO to consolidation with ATRA/chemotherapy and reported improved outcomes in the groups receiving ATO [26]. The APML4 study added ATO to ATRA and anthracycline induction and eliminated chemotherapy from consolidation, utilizing 2 cycles of ATRA/ATO followed by 2 years of maintenance therapy. Investigators reported a 95% hematologic CR following induction and a 2-year OS of 94% [25]. An update presented at the 2013 Rome APL meeting reported a sustained 5-year OS of 94% [29]. The APL0406 trial built on data obtained from these previous studies. In this study, newly diagnosed patients with standard risk APL were randomized to ATRA/ATO for induction and consolidation therapy or induction therapy

with ATRA/idarubicin followed by ATRA/chemotherapy consolidation and 2 years of maintenance therapy. At 34.4-month follow-up, EFS was 97% in the ATRA/ATO group and 86% in the ATRA/chemotherapy group. Additionally, the ATRA/ATO group had improved OS compared to the ATRA/chemotherapy group (99% vs. 91%). This improvement in OS was mostly due to reduced treatment related toxicity rather than death from relapse. Specifically, rates of neutropenia and infection were higher in the ATRA/chemotherapy group; the incidence of hepatotoxicity and QTc prolongation were increased in the ATRA/ATO group, but in the majority of cases, these findings were reversible with ATO withdrawal. Therefore, not only was toxicity improved with ATRA/ATO, relapse rates were similar between groups as well implying that disease free survival was not compromised by less intensive therapy [12]. Additionally, with elimination of anthracyclines from the regimen, long-term side effects including cardiac toxicity and secondary myeloid neoplasms may be reduced. Based on this study, ATRA/ATO is now a recommended upfront regimen for standard risk APL while previously it was recommended in the relapsed setting or in patients unable to receive anthracyclines [30]. Notably, the role of ATO based induction in high-risk APL or in patients over age 70 was not addressed by this trial.

Consolidation Therapy

Consolidation regimens in an anthracycline based induction approach vary and recent studies have focused on a risk-adapted strategy when choosing consolidation agents. The LPA96 and LPA99 studies used the same AIDA (ATRA/idarubicin) induction regimen but varied the consolidation regimen based on risk of relapse [15, 18, 19]. The LPA 99 study specifically confirmed the benefit of ATRA use in consolidation (in addition to intensified chemotherapy), most notably in the intermediate and high-risk groups. The French APL 2000 study and the LPA 2005 study further defined the role of cytarabine in consolidation therapy [20, 31]. A comparison of the LPA 99 trial and the French APL 2000 study showed that cytarabine given in induction/consolidation was beneficial in the high-risk group but did not benefit the standard-risk group [17].

More recently, the question of ATO use in consolidation has been explored. The APML4 study used ATO/ATRA/idarubicin in induction followed by 2 cycles of ATRA/ATO in consolidation in all risk patients and reported a 2-year OS of 93.2% [25]. The North American Intergroup trial C9710 confirmed a benefit of ATO use in consolidation in all patients [26]. The APL0406 study also used ATO/ATRA for consolidation in the study arm and reported EFS rates and OS rates superior to the standard chemotherapy arm [12]. In summary, several consolidation regimens are appropriate, and a risk-adapted strategy should be used when selecting therapy in APL. However, it should be emphasized that regimens should generally not be mixed and matched but rather followed in entirety per protocol from induction through maintenance. This allows the possibility of optimal results as demonstrated in the corresponding trials.

Role of maintenance

In contrast to other subtypes of AML, consolidation has traditionally been followed by two years of maintenance therapy with ATRA, 6-mercaptopurine and methotrexate [13]. Now that ATO is being used in induction and/or consolidation, need for maintenance has been

questioned. In the phase II study published by Estey, low risk patients received ATRA/ATO for induction followed by intermittent ATRA/ATO for a total of 28 weeks after CR was confirmed. High-risk patients also received gemtuzumab ozogamicin (GO). Maintenance therapy was eliminated [24, 27]. At a median follow-up of 99 weeks, OS was 85%. Not only did this study suggest that chemotherapy may not be required to achieve cure in APL, it also questioned the role of maintenance therapy. A phase III SWOG study sought to examine the role of maintenance therapy. In this trial, standard-risk patients received a standard induction and consolidation regimen including ATO and were then randomized (if in molecular remission) to one year of maintenance therapy vs. observation. Although the study was closed due to slow accrual, at 22.7-month follow-up, the OS in all patients was >93% and no relapses were noted in either group [32]. The APL 0406 study of ATRA/ATO for induction confirmed that survival and relapse rates are not compromised by deletion of maintenance therapy when ATO is used in induction and consolidation. However, median follow-up was only 34.4 months and longer follow-up may be needed in all of these studies to ensure that maintenance therapy can indeed be eliminated [12].

Complications and management of high risk APL

Increased Early Death Rate

20–25% of APL patients present with WBC over 10,000/ μ L, and these high-risk patients have both a higher early death rate (EDR) and an increased risk of relapse. They typically present with more severe coagulopathy and have higher rates of life threatening bleeding [33]. Even in the post-ATRA era, EDR has been reported between 5–20% in this subgroup of patients [13, 14, 19, 27, 33]. This rate may even be an underestimate as it only encompasses patients treated at academic centers and/or stable enough for clinical trial enrollment. One single center study reviewed data on their APL patients not enrolled on clinical trials and found an EDR of 21% compared to 3% in patients enrolled on clinical trials [34]. Patients not enrolled tended to have higher WBCs and lower platelet counts. Despite major advances in APL therapies, the EDR remains high, mostly due to hemorrhagic complications. In the Swedish APL registry, reported EDR was 29% and death occurred more commonly in elderly patients and patients with poor performance status. The majority of early deaths were due to bleeding, followed by cardiopulmonary failure and sepsis [35]. In a retrospective study of APL patients treated at 5 centers, including our institution, the death rate in the first 30 days was 11% and 61% of these deaths were attributable to hemorrhage. There was an increase in hemorrhage following delay of ATRA administration, resulting in increased EDR only in the high risk group [36]. Other studies suggest that early ATRA may not necessarily decrease the EDR however [37]. Despite this, ATRA should still be administered at first suspicion of APL [38]. The importance of aggressive transfusion support is also important. We suggest maintaining a platelet count greater than 30,000–50,000/ μ L and fibrinogen level more than 150 mg/dL [39]. Although ATRA does reverse the coagulopathy generally in a few days, aggressive blood product support is necessary in the days following suspicion and diagnosis of APL to decrease the EDR [40].

Additionally, the risk of developing APL differentiation syndrome (DS) increases with rising WBC count and is another cause of early death [41]. DS is characterized by fevers and respiratory distress as well as interstitial pulmonary infiltrates, pleural effusions, weight gain and lower extremity edema [42]. This syndrome is often mistaken for pneumonia, volume overload or alveolar hemorrhage. Prophylaxis with high dose dexamethasone was used in the APL 2000 trial and led to a decrease in DS related deaths to 3.9% compared to 5.7% reported in the earlier APL 93 trial [43]. If not used preemptively, steroids should be started at the earliest sign of DS. If symptoms are life threatening, ATRA or ATO should be temporarily discontinued until symptoms resolve. Prophylactic steroid use is recommended in high-risk patients and should be strongly considered in patients treated with ATRA/ATO for induction as was used preemptively in patients treated with ATRA/ATO on the GIMEMA APL 0406 trial [30].

While most patients with APL present with lower WBCs compared to other AML subtypes, 20–25% will present with a WBC over 10,000/ μ L and 5% or fewer patients will present with a WBC greater than 50,000/ μ L [41]. Leukapheresis is generally not recommended in APL given early reports of death following this procedure [44]. Additionally, placement of a central venous catheter necessary for leukapheresis is not recommended given the underlying coagulopathy. Cytotoxic chemotherapy in combination with ATRA should begin promptly in this high-risk group. Hydroxyurea can also be used as a temporizing measure to control leukocytosis [12].

Increased Relapse Rates

Relapse rates are also greater in the high-risk group. Several studies have shown cytarabine-containing regimens used during induction or consolidation lead to higher OS and lower relapse rates in high-risk APL [17, 31]. Additionally, maintenance therapy is recommended in the high-risk group. The APL 93 trial showed a clear benefit for combined maintenance therapy, most noticeable in high-risk patients [13]. A comparison of the APL 93 trial and APL 2000 trial showed that systematic maintenance therapy as received in the APL 2000 trial was the strongest factor associated with improved OS in the high-risk group [43].

The role of ATO is less well-defined and is not routinely recommended for induction therapy in high-risk groups, apart from in the APML4 regimen. Its use in consolidation is better studied. The North American Intergroup trial C9710 randomized patients to consolidation with ATO following standard daunorubicin/ATRA/cytarabine induction and showed a benefit in all risk groups receiving ATO. Notably, DFS was similar between the standard risk group that did not receive ATO and the high-risk group that received ATO suggesting that addition of ATO may partially overcome the negative prognosis associated with high-risk disease [26].

In regards to CNS relapse, the cumulative rate of CNS relapse in high-risk APL patients is 5% [45]. Outcomes in patients with CNS relapse are poor and given the increased incidence in high-risk APL, some authors are proponents for prophylactic intrathecal therapy; however, others do not consider this a standard recommendation, given that the number to treat to have a benefit is quite large [38, 45–47]. Furthermore, cytarabine and ATO both cross the blood-brain barrier and may obviate the need for prophylactic intrathecal therapy.

Considerations in elderly patients with APL

APL is relatively uncommon in patients over age 60, representing only 15–20% of patients diagnosed [48]. The EDR is higher in this cohort due to greater comorbidities compared to their younger counterpart. In a Swedish Leukemia registry study, the EDR was 29% in all age groups but 50% in patients over age 60 [35]. Similarly, a study using the Surveillance, Epidemiology, and End Results (SEER) data from the United States reported an EDR of 24% in APL patients over age 55 [49]. Although EDR and treatment related mortality are higher in this subgroup, patients tend to present with lower risk disease and have lower rates of relapse. The European APL group reviewed outcomes in elderly patients from the APL 93 trial and reported a 4-year OS of 57.8% in elderly patients compared to 78% in younger patients. Elderly patients achieved lower rates of CR (86% vs. 94%) and more died in CR (18.6% vs. 5.7%), mostly as a result of complications during consolidation and maintenance therapy. However, 4-year relapse rates were lower in the elderly group compared to the younger cohort (15.6% vs. 23.2%) [50]. Results from other studies report similar findings in their elderly cohorts: lower CR rates, higher death rates while in CR, mostly as complications from myelosuppression, resulting in worse OS [51, 52]. In an attempt to decrease these treatment related deaths, the GIMEMA group amended their AIDA protocol to decrease the consolidation courses in elderly patients from three cycles to one [53]. This resulted in an improved OS in the amended protocol cohort compared to the original cohort due to a decrease in treatment related death.

ATO has a more favorable side effect profile compared to conventional chemotherapy and is an attractive option in this elderly cohort that is particularly susceptible to treatment related toxicities. Most studies that use ATO +/- ATRA in the upfront or relapsed setting do not report specifically on outcomes in the elderly. The Chinese group used single agent ATO for remission induction and post-remission therapy for up to 4 years in patients over age 60. 88% achieved CR and 10-year rate of relapse, OS and cause-specific survival were 10.3%, 69.3% and 84.8%, respectively. Post-remission therapy with ATO was well tolerated, and no ATO-related deaths occurred. The main side effect from therapy was leukocytosis with resulting DS which was successfully managed in all patients. On ten-year follow up, there was no increased rate of malignancy or arsenic poisoning identified [54].

GO has also been studied in elderly patients and shown to be efficacious [27, 55, 56]; however, its approval was withdrawn from the US market and the ability to utilize GO is severely limited. The APL 0406 trial showing superiority of ATRA/ATO over ATRA/chemotherapy is particularly relevant for elderly APL patients; however, the upper limit of age enrollment was 71 years old. The original publication did not stratify patients by age but the authors recently submitted a letter addressing outcomes in patients ages 60–70. They report similar findings seen in the younger cohort including improved EFS and improved toxicity profile in the ATRA/ATO arm. These findings were non-significant but the numbers analyzed were small [57]. Given the low toxicity of ATRA/ATO, this regimen may be especially appropriate for the elderly population but further studies are required.

Considerations in relapsed APL

With current treatment regimens, approximately 10% of APL patients will relapse [46]. Most studies use ATO alone or in combination with other agents in the relapsed setting [22, 23, 58–62]. Soignet reported results of 40 patients with relapsed APL. Patients received ATO for induction followed by consolidation and maintenance with ATO. 85% of patients achieved CR; at 18 months follow-up, the OS was 66% and relapse free survival was 56% [58]. Shigeno used single agent ATO for induction and consolidation for 34 patients with relapsed APL; they reported a 2-year OS of 56% [61]. One small trial by French investigators randomized relapsed patients to ATRA/ATO or ATO alone [60]. Outcomes were similar between groups leading its authors to conclude that there was no benefit to adding ATRA to ATO. Current guidelines suggest ATO +/- ATRA for treatment of relapsed disease; however, now that ATRA/ATO is recommended first line, it is unclear how this will affect management of relapsed disease [30]. A retrospective report was recently published of 25 patients with relapsed APL who had been exposed to upfront ATRA/ATO in addition to cytotoxic agents. Patients received a variety of reinduction regimens at relapse including ATRA/ATO or chemotherapy regimens. The authors reported a 40% CR rate in the patients receiving ATRA/ATO; however, complete molecular remission was low and relapse remained high [63]. For patients with relapsed APL after prior ATRA/ATO exposure, a trial of re-induction with ATRA/ATO is appropriate if sufficient time has passed from last ATO exposure (6–12 months). Alternatively, standard ATRA/chemotherapy regimens can be utilized. Once CR is obtained, we would recommend following guidelines for consolidation with an autologous or allogeneic stem cell transplant (SCT) depending on molecular status.

After attaining a second remission, CSF evaluation and intrathecal chemotherapy is recommended given the risk of CNS involvement in relapsed APL. Autologous SCT is also recommended as post-remission therapy in patients in complete molecular remission (CMR). In a retrospective study of 37 patients with relapsed APL, patients received induction and consolidation with ATO alone or ATO in combination with other agents. Thirty-three patients (89%) achieved a second remission and of these, 14 received an autologous SCT and 19 received monthly ATO +/- ATRA for 6 months. At a median 32-month follow-up, EFS was 83% in the transplant arm compared to 34.4% in ATO +/- ATRA arm [64]. Autologous SCT has been compared to allogeneic SCT in the relapsed setting as well. In a retrospective study by French investigators, 122 patients with relapsed APL in second remission received autologous SCT or allogeneic SCT. Seven-year RFS and OS were 79.4% and 59.8% in the autologous SCT group compared to 92.3% RFS and 51.8% OS in the allogeneic SCT group. OS was significantly lower in the allogeneic SCT group secondary to increased treatment related toxicity [65]. Investigators from MD Anderson retrospectively reviewed outcomes in 40 relapsed APL patients undergoing autologous SCT, allogeneic SCT or chemotherapy alone. They found no difference in EFS or OS between groups but the numbers were small and there was a trend toward improved outcomes in the autologous SCT group [66]. Therefore, autologous SCT in second CMR is recommended in patients able to receive the high dose chemotherapy required for conditioning. Allogeneic SCT should be reserved for patients that do not achieve CMR. In

this group, the graft vs. leukemia effect leads to a decreased rate of relapse. If patients are not transplant eligible, consolidation with ATO or enrollment on a clinical trial is recommended [30].

New Drugs and Formulations

Oral Arsenic

ATO has only been available in IV forms until recently. There is considerable interest in developing an oral formulation of ATO. This would have particular relevance in the long consolidation phase in which patients must come to the office daily for IV ATO. A recent phase III randomized trial compared IV ATO to a new oral formulation of ATO and demonstrated non-inferiority of oral ATO to IV ATO, showing comparable rates of CR, OS and adverse events [67]. This oral form of ATO is not currently available in the United States, but there is interest among investigators throughout North America, Europe, and Australia in developing an oral formulation of ATO.

Liposomal ATRA

Lipo-ATRA, a liposomal form of ATRA, was initially studied with the intent of trying to eliminate chemotherapy in APL treatment. In a study with healthy volunteers, plasma levels of lipo-ATRA were 15-fold elevated compared to oral ATRA and the half-life was also prolonged [68]. Initiated in 1997 prior to the advent of ATO, a prospective trial was performed using lipo-ATRA alone in 34 patients with untreated APL and results were compared to historical controls who had received the AIDA regimen. The CR rate in the standard risk group was 92%, similar to CR rates achieved in historical controls; however, in the high-risk group, the CR rate was only 38%, significantly lower than matched historical controls [69]. At 13-year follow up, the authors reported an OS of 65% and no secondary malignancies noted [70]. Lipo-ATRA is not routinely used or readily available but could be considered in situations where oral ATRA is not feasible.

Tamibarotene

Tamibarotene is a synthetic retinoid, developed and approved in Japan for treatment of relapsed/refractory APL prior to widespread use of ATO in the relapsed setting. ATRA resistance is uncommon but when it does occur, is postulated to be secondary to RAR- α mutations, increased levels of cellular retinoic acid binding protein (CRABP), accelerated elimination of ATRA and other genetic mutations [71, 72]. Tamibarotene exhibits more potent differentiation ability compared to ATRA and is also more specific in its binding. Tamibarotene only binds to RAR- α and RAR- β while ATRA also binds to RAR- γ (present on dermal epithelium). This difference in binding suggests that tamibarotene may be associated with fewer rashes and other skin toxicities than ATRA. Additionally, tamibarotene, unlike ATRA, does not have a high binding affinity to CRABP, suggesting it may be more active in an ATRA-resistant setting. [73]. One small Japanese study was performed in which 24 evaluable patients with relapsed APL following ATRA exposure received tamibarotene. 58% of patients achieved a CR. The most significant serious side effect was hyperlipidemia but overall, treatment was well tolerated [74]. Data with this drug is limited in the US and Europe, used in the relapsed/refractory setting [75, 76]. A phase II

clinical trial (STAR-1), evaluating tamibarotene in the relapsed setting following prior ATRA and ATO therapy, was initiated with results currently pending.

Conclusions

Treatment for APL is one of the major success stories in oncology. APL was once the most deadly form of AML and is now the most treatable. Cure rates have improved significantly after ATRA was added to chemotherapy, and with the advent of ATO in combination with ATRA, it is now possible to cure many patients without chemotherapy. Given that APL more commonly occurs in younger patients, decreasing secondary malignancies by avoidance of chemotherapy is of paramount importance. Furthermore, utilization of ATO/ATRA decreases treatment related toxicity and may be particularly beneficial for older adults. EDR continues to be a pressing problem, even at experienced centers, and maintaining a high suspicion of APL, employing aggressive blood product support, and initiating ATRA early should be utilized to minimize early deaths. Further study is required to determine therapeutic options for recurrent disease after initial ATRA/ATO based therapy. New drug combinations and novel drug formulations continue to be developed with the goal of optimizing APL therapy, minimizing toxicities and making therapy more convenient for patients.

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Table 1

Cooperative group studies using non-ATO based regimens

Group	Year	N	Induction	Consolidation	Maintenance	CR	D(E)FS (2 year unless otherwise specified)	OS (2 year unless otherwise specified)
European APL 93 ¹³	1999	413	ATRA → DNR/AraC vs. ATRA + DNR/AraC	DNR/AraC	None vs. ATRA vs. 6-MP/MTX vs. ATRA/6-MP/MTX	92% both arms	ATRA → chemo: 77% ATRA+chemo: 84% EFS	ATRA → chemo: 81% ATRA+chemo: 84% OS also improved in ATRA/chemo maintenance group
GIMEMA 93 ¹⁴	1997	253	Ida+ATRA	AraC/Ida/MTZ/etoposide/6-TG	None vs. ATRA vs. 6-MP/MTX vs. ATRA/6-MP/MTX	95%	79% EFS	87%
PETHEMA LPA 94 ¹⁵	1999	123	Ida+ATRA	Ida/MTZ	6-MP/MTX/ATRA	89%	79% EFS	82%
PETHEMA LPA 99 ¹⁹	2004	426	Ida+ATRA	Ida/MTZ (+ATRA in intermediate/high risk groups)	6-MP/MTX/ATRA	90%	87% 3 y DFS	85% at 3 y
European APL 2000 ²⁰	2006	340	DNR+ATRA +/- AraC	DNR +/- AraC	6-MP/MTX/ATRA	+AraC: 99% No AraC: 94%	+AraC: 93% No AraC: 77% EFS	+AraC: 98% No AraC: 89.6%
PETHEMA LPA 2005 ³¹	2010	404	Ida+ATRA	Ida/ATRA/MTZ (+AraC in high risk group)	6-MP/MTX/ATRA	92.5%	92% 3 y DFS	89% at 3 y

Abbreviations: ATRA: all-trans retinoic acid; DNR: daunorubicin; araC: cytarabine; 6-MP: 6-mercaptopurine; MTX: methotrexate; Ida: idarubicin; MTZ: mitoxantrone; 6-TG: 6-thioguanine

Table 2

Studies using ATO based regimens

Author	Year	N	Induction	Consolidation	Maintenance	CR	D(EFS (2 year unless otherwise specified))	OS (2 year unless otherwise specified)
Shen et al ²⁸	2004	61	1 ATRA	DNR/AraC/HA in all groups	1 ATRA/6-MP/MTX	>90% in all arms	1 13 months	Not reported
			2 ATO		2 ATO/6-MP/MTX		2 16 months	
			3 ATRA + ATO		3 ATRA/ATO/6-MP/MTX		3 20 months DFS	
Ravandi et al ²⁷	2009	82	ATRA/ATO (+GO in high risk group)	ATRA/ATO	none	92%	~80% EFS	~85%
Powell et al ²⁶	2010	481	ATRA/AraC/DNR	ATRA/DNR vs. ATRA/DNR/ATO	ATRA vs. ATRA/6-MP/MTX	90% in both arms	90% in ATO arm 70% in non-ATO arm DFS	86% in ATO arm at 3y 81% in non-ATO arm at 3y
Iland ²⁵	2012	124	ATRA/Ida/ATO	ATRA/ATO	6-MP/MTX/ATRA	95%	97.5% DFS	93%
Lo-Coco ¹²	2013	156	ATRA/ATO vs. ATRA/Ida	ATO/ATRA vs. Ida/ATRA/MTZ	None (ATRA/ATO arm) vs. 6-MP/MTX/ATRA (ATRA/Ida arm)	ATRA/ATO: 100% ATRA/chemo: 95%	ATRA/ATO: 97% ATRA/chemo: 86% EFS	ATRA/ATO: 99% ATRA/chemo: 91%

Abbreviations: ATRA: all-trans retinoic acid; ATO: arsenic trioxide; DNR: daunorubicin; AraC: cytarabine; HA: homoharringtonine; 6-MP: 6-mercaptopurine; MTX: methotrexate; GO: gentuzumab; ozogamicin; Ida: idarubicin; MTZ: mitoxantrone; MTX: methotrexate