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How I Treat Children and Adolescents with Acute Promyelocytic Leukaemia

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Summary

Acute promyelocytic leukaemia (APL) is a rare subtype of acute myeloid leukaemia. The outcome of paediatric APL has improved substantially over the past 20 years; cure rates above 80% are expected when all-*trans* retinoic acid (ATRA) is given with anthracycline-based regimens. The presenting features of paediatric APL may include severe bleeding and thrombotic complications, which contribute to the high early death rate. The incidence of leucocytosis and the microgranular subtype is greater in paediatric than adult APL, and children experience greater ATRA-related toxicity. It is crucial to begin ATRA therapy and intensive platelet and fibrinogen replacement on first suspicion of APL. Recent risk-adapted therapeutic trials have shown that patients at greater risk of relapse benefit from the introduction of high-dose cytarabine during consolidation. Combination therapy with ATRA and arsenic trioxide provides very effective frontline treatment and may reduce the need for subsequent anthracycline therapy.

Keywords

leukaemia; promyelocytic; paediatric; arsenic trioxide; ATRA

Introduction

Acute promyelocytic leukaemia (APL) arises from clonal expansion of cells arrested at the promyelocyte stage (De Botton *et al*, 2004; Gregory & Feusner, 2003). The diagnostic hallmark is the translocation t(15;17)(q22;q21.1) fusing the genes encoding promyelocytic leukaemia protein (*PML*) and retinoic acid receptor alpha (*RARA*), generating the PML-RARA oncoprotein (Lo Coco *et al*, 2008). PML-RARA directly binds to a nuclear

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Author contributions:

Oussama Abl performed the literature search, outlined the manuscript, designed the tables, provided details on Cases 1, 3, 4, 5 and 6, and wrote most sections of the manuscript. Raul Ribeiro provided Case 2, performed additional literature searches, wrote the Introduction and Management of Relapse sections, and was responsible for final revision and review of the manuscript.

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corepressor complex and represses gene transcription. It cannot dissociate from the corepressor complex at physiological retinoic acid levels (Grignani *et al*, 1998).

The complete remission (CR) rate of APL is now >90%, and the cure rate is >80% (Sanz *et al*, 2010). Moreover, refractory disease and relapse can now be detected early (at the molecular level), and management can be adapted to diverse clinical scenarios. Childhood APL has customarily been treated on adult protocols. Although the overall outcome appears similar, there are clinical, biological, and therapeutic considerations unique to paediatric APL (De Botton *et al*, 2004). Here we present six real-life case scenarios. These cases were managed at different time points by different physicians at two tertiary-care institutions. Whilst not examples of ideal clinical practice, these cases illustrate the issues encountered in the diagnosis, risk stratification, treatment, and management of childhood APL and its complications.

Case 1

An 11-year-old Asian boy with a history of headaches, gingival bleeding and bruising presented with a white blood cell (WBC) count of $83.6 \times 10^9/l$ with 90% blasts. His haemoglobin concentration (Hb) was 62 g/l, platelet count $27 \times 10^9/l$, fibrinogen 0.8 g/l, international normalized ratio (INR) 1.7, partial thromboplastin time (PTT) 24 s, serum D-dimer > 400 µg/l, urate 500 µmol/l, lactate dehydrogenase (LDH) 764 u/l, creatinine 60 µmol/l, and albumin 38 g/l. His blood smear showed many abnormal promyelocytes with bilobar nuclei and cytoplasmic granules; some contained multiple Auer rods. Flow cytometry showed expression of CD13, CD33, CD34, CD2, MPO, and HLA-DR by circulating blasts. Fluorescence *in situ* hybridization revealed the t(15;17)(q22;q21.1) (*PML-RARA*), and reverse transcription polymerase chain reaction (RT-PCR) identified the fusion transcript (BCR3 isoform) and *FLT3* internal tandem duplication (*FLT3*-ITD). Eight hours after presentation, he experienced generalized tonic-clonic seizures, right-sided hemiparesis, and decreased consciousness. Brain magnetic resonance imaging (MRI) showed extensive infarction in the left middle cerebral artery (MCA) area and multiple infarcts in right temporal and parietal white matter. The seizure activity continued, and he was admitted to intensive care, where he was intubated (Glasgow coma, 10). Initial treatment comprised idarubicin (12 mg/m²/day IV), fractionated heparin (24–48 units/kg/h) and aggressive platelet and fibrinogen replacement. All-*trans* retinoic acid (ATRA; 25 mg/m²/day via nasogastric tube) was not initiated until 20 h after presentation, due to the patient's unstable clinical condition and delay in obtaining ATRA preparation for nasogastric tube administration. Forty-eight hours after the start of therapy, his neurological status deteriorated rapidly, and computerized tomography (CT) showed a new infarction in the right MCA area with progression of the left MCA infarction and left uncal herniation. He died less than 96 h after presentation. Postmortem examination revealed thrombotic endocarditis, brain and kidney thromboembolic infarcts, and arterial and venous thrombosis and haemorrhage in multiple organs. Myeloperoxidase-positive APL infiltrates were observed in bone marrow and in many organs and blood vessels.

Case 2

An obese 13-year-old girl presented with altered mental status, generalized weakness, blurred vision, and somnolence. Her temperature and vital signs were normal. She was stuporous but responsive to vigorous stimulation, was combative and disoriented when aroused, and could not follow commands. Pupils were reactive and equal and gaze was normal. Bilateral papilledema and retinal haemorrhage were noted, without focal motor abnormality. The WBC count was $93.7 \times 10^9/l$ with 88% blasts, some containing Auer rods, and occasional faggot cells. Hb was 63 g/l and platelets, $45.0 \times 10^9/l$. She had a prolonged INR (1.7) and low fibrinogen level (0.14 g/l). Cytogenetics revealed the t(15;17)(q24;q21.1), and molecular analysis demonstrated the *PML-RARA* fusion transcript and *FLT3-ITD*.

In intensive care, she received aggressive platelet and fibrinogen replacement and started ATRA and idarubicin. CT imaging showed no acute haemorrhage or midline shift. Brain MRI with angiography showed bilateral arterial infarcts in the parietal, occipital, and frontal lobes. Dexamethasone was started, but heparin was withheld to prevent bleeding. Her induction course was complicated by respiratory distress (ATRA differentiation syndrome), seizures, and pseudotumour cerebri (PTC). She slowly recovered and began consolidation therapy with ATRA and arsenic trioxide (ATO) (cycle I), ATRA, high-dose cytarabine (Ara-C), and mitoxantrone (cycle II), ATRA and idarubicin (cycle III), and ATRA, high-dose Ara-C, and idarubicin (cycle IV), per the Children's Oncology Group (COG) AAML0631 protocol (NCT00866918). Quantitative PCR revealed no *PML/RARA* after cycle I. She was undergoing maintenance therapy without neurological sequelae at the time of this report.

These two cases illustrate unique aspects of paediatric APL and the challenges of managing severe coagulopathy at presentation, which remains a major cause of early death.

Presentation and diagnosis

Paediatric APL is diagnosed at a median age of 12 years (De Botton *et al*, 2004; Testi *et al*, 2005; Ortega *et al*, 2005; Bally *et al*, 2012); diagnosis at age <1 year is rare (Gilbert *et al*, 1987). Female sex predominates among children but not adults (De Botton *et al*, 2004), and high body mass index is more frequent in APL than other acute myeloid leukaemia (AML) subtypes (Feusner *et al*, 2006). Case 1 had the microgranular variant of APL (M3v), which is more common in children (11%–32%) (De Botton *et al*, 2004; Testi *et al*, 2005). M3v is characterized by multilobar nuclei, scant granules and infrequent Auer rods (Figure 1A, B) (Rovelli *et al*, 1992), while classic APL blast cells, found in 75%–85% of adults, are hypergranular with bilobar nuclei, abundant cytoplasmic granules, and prominent Auer rods (Figure 1C, D). Both adult and paediatric APL often feature faggot cells containing multiple Auer rods. APL cells stain consistently with myeloperoxidase and Sudan black B (Rovelli *et al*, 1992). The APL immunophenotype is strongly myeloid (CD13, CD33, CD9, and CD65), and CD34 and HLA-DR are absent (Drexler 1987). However, M3v cases may express HLA-DR, CD34, and the T-cell-associated CD2. One study suggested that aberrant CD2 expression is associated with better initial treatment response (Guglielmi *et al*, 1998). A minority of APL cases show aberrant expression of Natural Killer (NK) cell-associated CD56, reportedly associated with greater risk of relapse in adults (Ferrara *et al*, 2000). The

PML-RARA isoforms BCR2/BCR3 and organomegaly are more frequent in childhood APL (De Botton *et al*, 2004). APL-associated coagulopathy contraindicates lumbar puncture at diagnosis (Vahdat *et al*, 1994); therefore, the true incidence of central nervous system (CNS) involvement at diagnosis is unknown. Although one small study described initial CNS leukaemia in 3/40 (7.5%) patients (Biondi *et al*, 1994), a larger more recent paediatric study reported a 5% incidence (4/75) (Creutzig *et al*, 2010); in other large paediatric series, lumbar puncture was not routinely performed at diagnosis (Testi *et al*, 2005; Ortega *et al*, 2005; Bally *et al*, 2012).

Unlike adults, children with APL, particularly the M3v subtype, often present with leucocytosis and numerous circulating blast cells (De Botton *et al*, 2004; Rovelli *et al*, 1992; Ortega *et al*, 2005). One large French study observed a higher median presenting WBC count in children < 12 versus ≥ 13 years of age (10.8 vs $2.6 \times 10^9/l$, respectively) (Bally *et al*, 2012).

The presenting WBC count has several implications. Leucocytosis ($WBC > 10 \times 10^9/l$) at presentation is associated with the risk of relapse and early mortality (Vahdat *et al*, 1994; Sanz *et al*, 2000). Further, leucocytosis at diagnosis or during treatment with ATRA or ATO is associated with differentiation syndrome (Rego & De Santis, 2011). Hyperleucocytosis, particularly $> 50 \times 10^9/l$, indicates a risk of pulmonary or intracranial haemorrhage. The mechanism is poorly understood but is likely to reflect a combination of procoagulant and inflammatory mediators (Breen *et al*, 2011). Hyperleucocytosis and associated microcirculatory hyperviscosity can cause severe leucostasis. The CNS and lungs are the most common sites of symptomatic leucostasis, although other organ systems can be affected (Ganzel *et al*, 2012). Administration of an anthracycline (idarubicin or daunomycin) with ATRA on day 1 or 2 is generally recommended for children with leucocytosis. Dexamethasone on day 1 appears to reduce brain oedema and inflammation, as in Case 2 (Rego & De Santis, 2011; Vahdat *et al*, 1994). Leukapheresis should be avoided to prevent catastrophic bleeding (Vahdat *et al*, 1994).

Coagulopathy at presentation

Children with APL commonly present with coagulopathy. Approximately 80% of patients have a prolonged INR, elevated fibrin split products, low fibrinogen, and thrombocytopenia suggesting disseminated intravascular coagulation (DIC). Coagulopathy is often exacerbated by thrombocytopenia (reflecting reduced haematopoiesis), infection, and chemotherapy, which induce leukaemic-cell release of procoagulants (Breen *et al*, 2011). Severe haemorrhage and/or thrombosis cause a 20%–30% rate of early death in the developing world and a 5%–10% rate in developed countries, most frequently affecting the CNS and lungs (de la Serna *et al*, 2008). CNS bleeding during induction chemotherapy is an independent predictor of CNS relapse (Montesinos *et al*, 2009). The risk of bleeding is associated with leucocytosis, poor performance status, low fibrinogen, and elevated creatinine at presentation (Yanada *et al*, 2007). Before the introduction of ATRA (tretinoin), 73% of patients with the M3v subtype, but only 9% with classic APL, suffered early haemorrhagic death (Rovelli *et al*, 1992). During the ATRA era, the early death rate was reportedly 8.7% in childhood APL (<http://www.seer.cancer.gov>) and was 17.3% and 29% in

2 adult APL studies (Park *et al*, 2011; Lehmann *et al*, 2011). The apparently lower early death rate in children may partially reflect earlier referral to tertiary centres and fewer age-related comorbidities. As many as 10% of APL patients have arterial or venous thrombosis at presentation (Yanada *et al*, 2007); this complication is associated with leucocytosis, CD2 expression, BCR3 *PML-RARA*, *FLT3*-ITD, and greater risk of early death (Breccia *et al*, 2008).

Management of coagulopathy

Childhood APL is a medical emergency at presentation and should be managed in a tertiary paediatric centre. If APL is suspected, ATRA should be started immediately (Table I) to rapidly ameliorate coagulopathy (median, 4 days). Because bleeding is the main cause of early mortality, aggressive blood product support guided by frequent coagulation studies should commence promptly. Available guidelines recommend maintaining a platelet count of $30\text{--}50 \times 10^9/\text{l}$ and fibrinogen of $1\text{--}1.5 \text{ g/l}$ (Breen *et al*, 2011), while the International Consortium on childhood APL (ICC APL-01) protocol (NCT01226303) recommends maintaining platelets $>50 \times 10^9/\text{l}$ and fibrinogen $>1.5\text{--}2.0 \text{ g/l}$. Although heparin partially inhibits coagulation in DIC, a retrospective study comparing heparin with antifibrinolytic agents in the pre-ATRA era showed no benefit of heparin in APL-induced coagulopathy (Rodeghiero *et al*, 1990). Routine heparin use was abandoned with the introduction of ATRA, which alleviates DIC. Similarly, antifibrinolytic agents are not recommended for APL. A recent PETHEMA (Programa para el Estudio y Tratamiento de las Hemopatías Maligna) study failed to show reduced bleeding in APL patients treated with tranexamic acid (de la Serna *et al*, 2008). Further, severe thrombosis has been documented when ATRA and tranexamic acid are combined (Levi *et al*, 2009). Recombinant factor VIIa has successfully controlled life-threatening bleeding, but is not routinely recommended (Zver *et al*, 2004). Our two cases highlight the need for consistent guidelines for heparin and corticosteroid use in cases of life-threatening coagulopathy. In Case 1, replacement of platelets, fibrinogen, and heparin did not prevent fatal progression, and ATRA was not started promptly. This case illustrates the importance of ensuring consistent ATRA availability and clinician awareness of the urgency of ATRA administration. Further, this **patient's presenting high-risk features, including hyperleucocytosis, suggest that a short course of dexamethasone be considered earlier in induction to ameliorate the associated systemic inflammatory response and possibly prevent APL differentiation syndrome**. Case 2 received no heparin, but dexamethasone was given to reduce inflammation after ischaemic brain insult. Until more is known about these thromboembolic mechanisms and their tissue consequences, we suggest that dexamethasone be considered and heparin be withheld when patients present with hyperleucocytosis and/or signs of intracranial thrombosis.

Differentiation syndrome

Differentiation syndrome (DS) is a severe, sometimes life-threatening complication of ATRA or ATO; it occurs only during active disease, commonly during induction chemotherapy (Rego & De Santis, 2011), and has a reported paediatric incidence of 7.5%–20% (De Botton *et al*, 2004; Testi *et al*, 2005; Ortega *et al*, 2005; Bally *et al*, 2012). Clinically, DS can cause respiratory distress, fever, weight gain, pleural and pericardial

effusions, cardiac failure, hypotension, and/or renal failure. DS can mimic pneumonia, acute respiratory distress syndrome, sepsis, and congestive heart failure. Its main pathogenesis is an excessive inflammatory response, with chemokine overproduction and leukaemic-cell expression of adhesion molecules.

Risk factors for DS include late chemotherapy initiation, initial WBC count $> 5 \times 10^9/l$, high serum creatinine, and obesity (Rego & De Santis, 2011; Breccia *et al*, 2008, 2012). Because DS can cause early mortality (historically, 7.8%–33%; Breccia *et al*, 2008), prompt recognition and early treatment are crucial. In a more recent adult study, 3.4% of early deaths were attributed to DS (Lehmann *et al*, 2011). At the earliest suspicion of DS, ATRA or ATO should be suspended and IV dexamethasone should be administered until symptoms and signs resolve (minimum, 3 days). The recommended adult dose of dexamethasone is 10 mg twice daily (Sanz *et al*, 2009). No dose has been established in children, but those reported range from 0.25 mg/kg/dose (IV or PO, twice daily; maximum single dose, 10 mg) on the COG-AAML0631 protocol (NCT00866918) to 5 mg/m² (IV twice daily) on the ICC APL-01 protocol (NCT01226303). ATRA or ATO can be resumed at 75% (COG-AAML0631, unpublished observations) or 50% (ICC APL-01, unpublished observations) of the previous dose after DS has resolved. If this dose is well tolerated, gradual escalation should be attempted. Supportive measures may be needed, especially for severe DS. On the PETHEMA protocols, furosemide was administered to treat peripheral and pulmonary oedema and acute renal failure (Sanz *et al*, 2010).

Prognostic factors and treatment

The leading predictors of relapse in adult and childhood APL are RT-PCR evidence of the *PML-RARA* transcript after consolidation chemotherapy (Diverio *et al*, 1998; Suzuki *et al*, 2001; Burnett *et al*, 1999) and/or initial WBC count $> 10 \times 10^9/l$ (Testi *et al*, 2005; Bally *et al*, 2012; Burnett *et al*, 1999) (Table II). A Children's Cancer Group study found initial WBC $> 5 \times 10^9/l$ predicted reduced survival (Gregory & Feusner, 2003), while initial WBC and platelet counts were associated with relapse in adults (Sanz *et al*, 2000). The prognostic value of *FLT3*-ITD remains unestablished (Gale *et al*, 2005; Arrigoni *et al*, 2003; Barragán *et al*, 2011). One large paediatric APL study found that *FLT3* mutations (40% of cases) were strongly related to presenting leucocytosis and death during induction (Kutny *et al*, 2012). Other reported prognostic markers (Table II) have no current impact (Breccia *et al*, 2012; Bassan *et al*, 1995; Tallman *et al*, 2010; Albitar *et al*, 1999; Gallagher *et al*, 1997; Ferrara *et al*, 2000).

Specific therapeutic strategies for paediatric APL are derived from adult trials that included children. During the early 1990s, ATRA was confirmed to induce morphological remission of newly diagnosed and relapsed APL (Huang *et al*, 1988; Castaigne *et al*, 1990; Warrell *et al*, 1991). The importance of ATRA in paediatric APL is underscored by the North American Leukemia Intergroup Trial (INT0129), which randomly assigned children to induction with daunorubicin and Ara-C versus ATRA; after two cycles of consolidation, those in CR were randomly assigned to maintenance with ATRA versus observation for 1 year. Patients randomized to ATRA induction, maintenance, or both had 5-year disease-free survival (DFS) of 48% versus 0% in all others (Gregory *et al*, 2009). More recently, ATRA

combined with an anthracycline yielded long-term event-free survival (EFS) of 70%–80% in adults (Table III) and children (Table IV) (Sanz *et al*, 2010; Testi *et al*, 2005; Ortega *et al*, 2005; Bally *et al*, 2012; Adès *et al*, 2010; Avvisati *et al*, 2011). Anthracycline is now administered on day 1 or 2 to counteract leucocytosis associated with ATRA or ATO. The Italian AIDA (ATRA and idarubicin) 0493 trial, the largest paediatric APL series (107 children) during the ATRA era, had a CR rate of 96% and 10-year overall survival (OS) and EFS of 89% and 76%, respectively (Figure 2); addition of low-dose 6-mercaptopurine (6-MP) and methotrexate during maintenance therapy improved molecular DFS (Testi *et al*, 2005). The Spanish PETHEMA-LPA 2005 study suggested that addition of high-dose Ara-C (1 g/m²/day for 4 days) to consolidation therapy reduced relapse in patients at high risk (Table III) (Sanz *et al*, 2010). Other European trials have confirmed this finding (Adès *et al*, 2006; Lo Coco *et al*, 2010), but it remains unclear whether Ara-C can replace anthracyclines.

Importantly, relatively high-dose anthracyclines (450–750 mg/m²) plus ATRA achieved high cure rates in adults (Table III) (Sanz *et al*, 2010; Avvisati *et al*, 2011) and children (Table IV) (Testi *et al*, 2005; Ortega *et al*, 2005), although the high cumulative anthracycline dose risked late cardiotoxicity (Lipshultz *et al*, 2008; Thomas *et al*, 2002). In the PETHEMA 2005 study, a lower anthracycline dose provided equivalent efficacy with less myelosuppression in patients at low and intermediate risk (Sanz *et al*, 2010). The recent Berlin-Frankfurt-Münster (BFM) AML 2004 study was the first to demonstrate high cure rates with lower (350–410 mg/m²) cumulative anthracycline doses (Creutzig *et al*, 2010). The European APL group treated adults, adolescents (13–18 years), and children (<12 years) with ATRA, daunorubicin, and Ara-C. All adolescents had excellent outcomes (100% CR, 20% relapse, 93.6% 5-year survival), but the 12 children aged <4 years experienced a 52% five-year incidence of relapse and greater toxicity. Adolescents had better 5-year OS than adults (93.6% vs 80.4%) (Bally *et al*, 2012).

ATO may provide a safer and perhaps more effective alternative to anthracyclines in children. The North American Leukemia Intergroup Study C9710 randomly assessed ATO therapy after ATRA and anthracycline induction (Table III). Three-year EFS was 80% in the ATO arm versus 63% in the standard arm. However, patients aged <15 years were not eligible for ATO consolidation (Powell *et al*, 2010). Zhou *et al* (2010) reported induction and post-remission therapy with ATO alone in 19 children; 17 (89.5%) achieved haematological CR, but two died early of intracranial haemorrhage. ATO therapy continued for 3 years, and 5-year OS and EFS (83.9% and 72.7%, respectively) were comparable to those with ATRA plus chemotherapy (Zhou *et al*, 2010). A group in India treated 11 children with eight cycles of ATO over 12 months; 10 patients showed haematological CR at a median of 48 days and molecular CR at a median of 81 days. After a median follow-up of 30 months (range, 4–62 months), OS was 91% and relapse-free survival was 81% (George *et al*, 2004).

Because of their possible synergy, ATRA and ATO offer a promising option. In adults, this combination induced CR more rapidly (25 days) than either agent alone (40 and 31 days, respectively), and the relapse rate was zero (vs. 21% with ATRA alone and 12% with ATO alone) (Shen *et al*, 2004). A Chinese study used four induction regimens in 65 children with APL: ATRA alone (40 patients), ATO alone (8), ATRA+ATO (15), and Ara-C alone (2). The

latter two patients died early. Overall CR and 5-year OS were 91% and 89%, respectively, and 5-year EFS was 78% (76.2% with ATRA alone and 86.2% with ATO, alone or with ATRA) (Zhang *et al*, 2008).

The most recent COG APL protocol (AAML0631) is based on the ICC-APL-01 study, which in turn was based on the Italian AIDA 0493 trial (Testi *et al* 2005) and the BFM-AML-98 study (Creutzig *et al*, 2010). Like current adult protocols, the trial reduces the cumulative dose of anthracyclines (355 mg/m² of daunorubicin equivalent for standard-risk and 405 mg/m² for high-risk APL) and uses ATO and high-dose Ara-C consolidation. All patients at high risk or who have residual *PML-RARA* at the end of consolidation cycle III receive a fourth cycle of consolidation. Active agents, such as ATO and Ara-C, may allow significant reduction of anthracyclines. For example, a recent adult study showed excellent early outcomes (2-year OS, 93.2%; 2-year failure-free survival, 88.1%) with ATO+ATRA induction and consolidation and substantially reduced anthracycline use (Iland *et al*, 2012). ATRA and ATO combination therapy has also been used at MD Anderson Cancer Center (MDACC) to treat newly diagnosed adult APL; those with presenting WBC count $10 \times 10^9/l$ also received gemtuzumab ozogamicin (GO) on day 1 of induction. This regimen produced a CR rate of 98%, 5-year EFS of 86%, and 5-year OS of 88% (Ravandi *et al*, 2009). Finally, the Italian and German Cooperative Groups' randomized trial (Gruppo Italiano Malattie Ematologiche dell'Adulto [GIMEMA]- Study Alliance Leukemia [SAL]- German–Austrian Acute Myeloid Leukemia Study Group [AMLSG]) in adults with standard-risk APL achieved a 2-year EFS of 97% after ATO+ATRA vs. 86.7% after ATRA plus chemotherapy; the latter group also experienced greater toxicity and more frequent early death and recurrence (Lo Coco *et al*, 2013).

Case 3

A 3-year-old boy with standard-risk APL began induction on the PETHEMA protocol (Ortega *et al* 2005) with intravenous idarubicin and oral ATRA. He vomited during the first two attempts to swallow ATRA capsules.

Oral administration of ATRA to young, critically ill children

ATRA is available only in capsules, and oral administration to young children can be challenging. When children are unable to swallow capsules, soften the capsule in warm milk in a medicine cup. After 2 minutes, allow the child to chew the capsule alone or in a spoonful of soft food. A nasogastric (NG) or gastroenteric tube (G-tube, preferably a button G-tube) should be placed if necessary. For tube administration, draw out the contents of the softened capsule with an oral syringe, mix with the milk, and draw the mixture into the appropriate syringe for tube administration. High serum ATRA levels have been reported after NG administration (Shaw *et al*, 1995).

ATRA administration to comatose children also poses a dilemma. Kueh *et al* (1999) reported success in administering sublingual ATRA to a comatose adult by squeezing the capsule contents onto the floor of the oral cavity; the patient was in cytogenetic CR on day 60 and remained disease-free for more than 3 years. The bioavailability of ATRA is similar in adults

and children; however, maximum plasma drug concentration ($C_{\max}$) is higher in children (Takitani *et al*, 2006).

Case 3, treatment summary

The patient was able to chew and swallow softened ATRA capsules in a spoonful of soft food. He was in molecular remission after 3 cycles of consolidation therapy and was receiving maintenance therapy at the time of this report.

Case 4

A 13-year-old girl with high-risk APL started induction therapy with ATRA and idarubicin. On day 4 she complained of severe headache. Brain MRI was unremarkable. Ophthalmic examination showed bilateral mild papilledema and retinal haemorrhage. Neurological findings were unremarkable and lumbar puncture showed elevated cerebrospinal fluid (CSF) pressure (45 cm H₂O) with a normal cell count.

ATRA neurotoxicity

ATRA-related fever and headache may be more pronounced in children than adults, and ATRA neurotoxicity is more frequent in children (Testi *et al*, 2005; Takitani *et al*, 2006). PTC, with severe headache, vomiting, blurred vision, and papilledema, is a common paediatric side effect. The main risk is irreversible vision loss if the condition is prolonged. PTC is reported in 9% of paediatric APL patients, most frequently in those aged <10 years (De Botton *et al*, 1998). Focal neurological signs (excepting cranial nerve IV palsy) are usually absent, CSF pressure is >20 cm H₂O, and brain imaging is normal. When PTC develops, ATRA should be withheld until it diminishes to grade 0/1 (mild headache). Acetazolamide can improve symptoms when given to children < 12 years of age at 8 mg/kg 3 times daily orally or by IV bolus and to children > 12 years as 250–375 mg 3 times daily. Periodic lumbar puncture for therapeutic CSF reduction, adjusted for age/size, can also be helpful. Upon resolution of symptoms, ATRA may be re-started at a 75% dose (prescribed by the COG-AAML0631 protocol, NCT00866918) or a 50% dose (prescribed by the ICC APL-01 protocol, NCT01226303). If the reduced dose is well tolerated, gradual escalation to the full dose should be attempted. This complication has also been associated with ATO (Galm *et al*, 2000). Because azole antifungal agents inhibit cytochrome P-450 mediated ATRA catabolism, their concomitant use with ATRA may increase ATRA plasma levels, increasing the risk of PTC and nephrotoxicity (Yarali *et al*, 2008).

The optimal paediatric dose of ATRA is not established, but adult studies using 45 mg/m²/day have included guidelines for dose reduction based on toxicity (Tallman *et al*, 1997). PTC and DS are more common in children, and many paediatric studies have shown that ATRA remains effective at 25 mg/m²/day, with a lower incidence of side effects (De Botton *et al*, 2004; Testi *et al*, 2005; Ortega *et al*, 2005). Available data also suggest that a half-dose of ATRA can be as effective as the standard dose of 45 mg/m²/day (Chen *et al*, 1996).

Case 4, treatment summary

The patient was started on dexamethasone and acetazolamide. ATRA was withheld for 3 days. Her symptoms rapidly improved, and ATRA and chemotherapy were resumed. Her visual fields and fundi were monitored closely. She was in molecular CR after 3 cycles of consolidation and is currently receiving maintenance therapy (daily 6-MP, weekly methotrexate, and ATRA 25 mg/m²/d, for 15 days every 3 months). She is tolerating ATRA well.

Case 5

A 6-year-old boy presented with relapsed APL 1 year after completing therapy. His bone marrow showed 11% blasts, and RT-PCR identified *PML-RARA*. His initial diagnosis had been standard-risk APL. He had undergone induction and consolidation with ATRA and anthracyclines and was in molecular CR after consolidation. He underwent 2 years of maintenance therapy with close molecular monitoring.

Management of relapse

General principles for relapse management are based on non-randomized adult studies and small paediatric series. An expert panel recommends pre-emptive ATO therapy during molecular relapse to avert marked hyperleucocytosis and potentially fatal DS (Grimwade *et al*, 2009), and coagulopathy with its risk of fatal haemorrhage (Sanz *et al*, 2009) that can accompany clinical relapse. ATO is well documented to induce second remission (~80% after two courses). Therefore, ATO-containing regimens are the preferred salvage therapy (Sanz *et al*, 2009), although low-dose 6-MP and ATRA have shown success in children (Dvorak *et al*, 2005).

ATO triggers PML-RARA degradation, transcription of RARA target genes, and promyelocyte differentiation; it induces release of mitochondrial cytochrome C, causing caspase activation and apoptosis of APL cells (Nasr *et al*, 2008). ATO toxicity is caused by upregulation of glutathione-related genes and enzyme activity. ATO's high affinity for sulfhydryl groups also inhibits glutathione reductase and glutathione peroxidase activity, causing exposure to reactive oxygen species (Chen *et al*, 2011).

ATO is generally well tolerated by children. The most common acute toxicities are leucocytosis, coagulopathy, DS, QTc prolongation, peripheral neuropathy, rash, oral mucosal dryness, hepatic dysfunction, headache, nausea, and oedema (George *et al*, 2004; Zhang *et al*, 2008). Chronic side effects observed with long-term maintenance include neutropenia, peripheral neuropathy, hyperpigmentation, and muscular atrophy (Zhou *et al*, 2010). ATO accumulation has been reported in hair, nails, skeletal muscle, heart, lungs and kidneys. Children may be at greater risk of chronic ATO toxicity because of their smaller body mass (Kapaj *et al*, 2006). At the start of ATO treatment, the WBC count, serum potassium and magnesium, and renal and liver function indicators should be monitored; the QTc interval should be monitored frequently. Frequent echocardiography is warranted during and particularly after chemotherapy.

GO is a calicheamicin-conjugated monoclonal antibody directed against CD33, which is highly expressed on APL cells. Lo Coco *et al* (2004) reported that single-agent GO is more effective when begun during molecular relapse vs. haematological relapse of APL. The combination of ATRA, ATO, and GO was evaluated at MDACC in 8 adults with relapsed APL; 7 patients were found to be in CR after a median of 39 days (range, 21–56 days). After follow-up 36 months, 6 patients remained in CR and 2 patients had died in CR (Aribi *et al*, 2007). The limitations of GO include allergic reactions, myelosuppression, and hepatic veno-occlusive disease. The latter is more common in patients who subsequently undergo haematopoietic stem cell transplantation (HSCT) (Kell *et al*, 2003).

Post-salvage consolidation therapy

Regardless of the agents used to induce second molecular complete remission (CR2), patients are likely to benefit from further consolidation with HSCT. Allogeneic HSCT carries less risk of relapse, while autologous HSCT carries less risk of transplant-related mortality (Dvorak *et al*, 2008).

Case 5, treatment summary

After two cycles of ATO (0.15 mg/kg/day IV over 2 h, 5 days/week, 5 weeks/cycle), the patient gained molecular CR. After conditioning with busulfan and cyclophosphamide, he underwent matched sibling-donor allogeneic HSCT that was complicated by bronchiolitis obliterans requiring steroid treatment for several weeks. He is currently in remission, 2 years post-HSCT.

Case 6

A 13-year-old boy presented with isolated CNS relapse. He initially had the *PML-RARA* BCR3 isoform without *FLT3*-ITD; lumbar puncture was not performed at diagnosis. Initial treatment comprised ATRA (45 mg/m²/d), daunorubicin (30 mg/m²/d, days 3–6), and Ara-C (200 mg/m²/d, days 3–9). When ATRA-induced PTC occurred during induction, acetazolamide was started and ATRA was withheld for a few days. After molecular CR on day 45, he underwent consolidation therapy with daunorubicin and ATRA. Maintenance therapy comprised daily 6-MP (90 mg/m²/d), weekly methotrexate (15 mg/m²), and ATRA (45 mg/m²/d, days 1–15 every 3 months). After 5 months of maintenance therapy he experienced ataxic gait and tremors. Lumbar puncture revealed WBC of $58 \times 10^6/l$ with blasts expressing *PML-RARA* transcript; CSF opening pressure was elevated (42 cm H₂O). His bone marrow aspirate showed morphological and molecular CR.

CNS relapse

Extramedullary relapse, most commonly in the CNS or skin, typically occurs within the first year after diagnosis and is managed as a systemic disease. The 3-year cumulative incidence of CNS relapse was 1.1% in a PETHEMA–European APL group joint study (Montesinos *et al*, 2009). Both groups reported more frequent CNS relapse (5% and 5.5%) with initial WBC $>10 \times 10^9/l$ (de la Serna *et al*, 2008), while a recent review showed a very low incidence of CNS relapse (0.92%) in children with standard-risk (WBC $<10 \times 10^9/l$) APL (Chow &

Feusner, 2009). Therefore, CNS prophylaxis may be considered for patients with high-risk APL or intracranial haemorrhage before or during induction (Montesinos *et al*, 2009). The Japanese APL group recommends intrathecal methotrexate or Ara-C as CNS prophylaxis (Ohno *et al*, 2003); it is unknown whether triple intrathecal therapy (i.e. methotrexate, hydrocortisone, Ara-C) adds benefit. High-dose Ara-C readily penetrates the blood-brain barrier and may therefore be combined with ATRA as CNS-directed consolidation therapy for high-risk APL.

The optimal treatment of isolated CNS relapse is less clear; treatment similar to that for molecular or morphological relapse is recommended. The ICC-APL 01 protocol (NCT01226303) recommends triple intrathecal therapy every 3 days until blast-cell clearance, followed by two triple intrathecal injections 7 days apart. Both ATRA and ATO have been used successfully as systemic treatment in CNS relapse (Burry & Seki, 2002; Patriarca *et al*, 2002). Arsenic CSF levels are 30%–50% of serum levels (Au *et al*, 2008), while ATRA penetrates the blood-brain barrier poorly. After IT chemotherapy has induced CNS remission, the ICC-APL 01 protocol recommends 2 cycles of high-dose Ara-C (3 g/m²/day), GO, and ATRA systemic chemotherapy. After consolidation, patients in molecular remission may proceed to autologous HSCT if PCR-negative stem cells have been harvested. PCR-positive patients are candidates for allogeneic HSCT.

Case 6, treatment summary

Remission was reinduced with triple intrathecal therapy (methotrexate 12.5 mg, hydrocortisone 12.5 mg, Ara-C 30 mg, twice/week for 3 weeks), IV high-dose Ara-C (3 g/m², 4 doses), and oral 6-MP. His CSF cleared after 6 injections. ATRA was avoided because of severe previous complications and ATO was unavailable. Salvage therapy was complicated by sinus venous thrombosis, coagulase-negative staphylococcal sepsis, and recurrent PTC despite the absence of ATRA. *PML-RARA*-negative peripheral stem cells were harvested after 2 months of reinduction. After conditioning with cyclophosphamide and total body irradiation, he underwent autologous HSCT and remains in remission 6 years later.

Molecular monitoring

Minimal residual disease (MRD) is an independent predictor of APL relapse. Children and adults treated on the Italian AIDA protocols were found to be predisposed to haematological relapse if they had detectable *PML-RARA* transcripts at the end of consolidation (Testi *et al*, 2005; Diverio *et al*, 1998). Similarly, in the UK Medical Research Council (MRC) ATRA trial, patients with MRD after 3 courses of consolidation had a significantly higher risk of frank relapse (57% vs 26% at 5 years) and death (57% vs 82%) than MRD-negative patients (Burnett *et al*, 1999). After relapse, most patients are MRD-negative by customary nested RT-PCR at the end of consolidation, but quantitative RT-PCR (qRT-PCR) offers more sensitive detection of the *PML-RARA* transcript (Santamaria *et al*, 2007). The German AML Cooperative Group reported a greater risk of relapse in patients whose *PML-RARA* transcript levels (measured by qRT-PCR) were not reduced by 3 logs during the first 3–4 months of therapy (Schnittger *et al*, 2003).

Molecular monitoring of MRD can be used to identify patients at high risk of frank relapse who may benefit from pre-emptive therapy. In the PETHEMA and GIMEMA trials, pre-emptive therapy **with ATRA plus high-dose Ara-C followed by HSCT appeared to offer a survival advantage**, as compared to treatment at the time of haematological relapse (Esteve *et al*, 2007; Lo Coco *et al*, 2002). The UK-MRC group showed rigorous sequential qRT-PCR monitoring to be the strongest predictor of relapse-free survival; when used to guide ATO pre-emptive therapy, it effectively reduced the risk of clinical relapse (Grimwade *et al*, 2009). **However it remains to be determined whether pre-emptive therapy significantly improves overall survival.** MRD monitoring is also helpful in guiding therapy after HSCT (Grimwade *et al*, 1998).

Grimwade *et al* (2009) showed bone marrow qRT-PCR to be 1.5-log more sensitive than peripheral blood PCR in guiding salvage therapy with ATO. Bone marrow is considered the “gold standard” for MRD assessment in APL, and bone marrow RT-PCR is recommended at the end of consolidation and then every 3 months for at least 3 years (Sanz *et al*, 2009).

Long-term toxicity—Of 1010 children with AML on the BFM-93 and -98 studies, 5% had subclinical or clinical cardiomyopathy after receiving a cumulative 300–400 mg/m² of anthracycline (Creutzig *et al*, 2007). Few long-term APL survivors required cardiac transplantation (Bally *et al*, 2012; Thomas *et al*, 2002). Late subclinical cardiotoxicity (mild diastolic dysfunction) was observed in 52% of adult survivors of APL treated on the AIDA 0493 and 2000 protocols (Pellicori *et al*, 2012). In the AML-BFM studies, the incidence of second leukaemia was 4% in patients with APL but <1% in those with other AML subtypes (Creutzig *et al*, 2010). Other studies have also suggested a high incidence of post-APL secondary leukaemia (Testi *et al*, 2005; Lengfelder *et al*, 2009). Children with APL may have constitutional factors that increase their sensitivity to topoisomerase II inhibitors, commonly used in frontline APL therapies. Longer follow-up is needed for accurate assessment of these late effects.

The long-term safety of ATO in children is unclear. Reported late effects include hyperpigmentation, neutropenia, muscular atrophy and peripheral neuropathy (Zhou *et al*, 2010). One study reported a significant association between children’s neurocognitive function (particularly IQ) and their chronic environmental ATO exposure (Rosado *et al*, 2007). Future ATO-based paediatric APL trials should include longitudinal assessment of neurocognitive outcomes.

Rare variants of APL

In < 5% of cases, *RARA* appears to be fused to an alternative partner; in children, this is most commonly nucleophosmin (*NPM1*) (Redner *et al*, 1996). Fusion genes involving *NPM1* and *NUMA1* (nuclear mitotic apparatus protein 1) indicate sensitivity to ATRA, while abnormalities involving *ZBTB16* (*PLZF*) and *STAT5B* indicate ATRA (Mistry *et al*, 2003) **and ATO (Strehl *et al*, 2013) resistance.** The *ZBTB16* -*RARA* leukaemias have morphological features intermediate between those of M2 and M3 and carry a worse prognosis than *PML-RARA* leukaemia; chemotherapy and/or ATRA do not usually induce CR (Redner, 2002). However, CR was reported in one *ZBTB16* -*RARA* case treated with

ATRA and granulocyte colony-stimulating factor (G-CSF) (Jansen & Lowenberg, 2001). In transgenic mice, *ZBTB16-RARA* cells are insensitive to ATO but respond to ATRA combined with a histone deacetylase inhibitor (Redner, 2002). The *NPM1-RARA* and *NUMA1-RARA* fusions may also predict insensitivity to ATO (Mistry *et al*, 2003).

Future directions—For newly diagnosed standard-risk APL, the front-line, chemotherapy-free ATRA/ATO combination (Lo Coco *et al*, 2013) is extremely encouraging and will probably become the generally established front-line regimen for these patients. The combination of ATRA, ATO, and GO for high-risk APL is being evaluated in the Southwestern Oncology Group 0535 study (NCT00551460). Oral arsenic is also very effective, and its combination with oral ATRA warrants further investigation (Au *et al*, 2012). Novel drugs, such as FLT3 inhibitors, histone deacetylase inhibitors and tamibarotene (a synthetic retinoid more potent and less toxic than ATRA) (Ohnishi, 2007) may offer options for patients with high-risk or refractory APL. Finally, better options for treating coagulopathy and reducing early death are urgently needed. Recombinant human soluble thrombomodulin (rTM), which enhances ATRA's antifibrinolytic and antileukaemic effects in APL cells, may hold promise when combined with ATRA (Ikezoe *et al*, 2012).

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Figure 1. Bone marrow smears from two children with APL and the t(15;17)(q22;q21.1) chromosomal translocation

A. Smear from a child with hypogranular acute promyelocytic leukaemia showing blast cells of various sizes (Wright-Giemsa stain). A few promyelocytes show fine azurophilic granules (arrow) **B.** Smear from the same patient shows intense myeloperoxidase staining **C.** Smear from a child with hypergranular acute promyelocytic leukaemia showing abundant azurophilic granules in the cytoplasm of leukaemic promyelocytes (Wright-Giemsa stain) and a promyelocyte with multiple Auer rods (“faggot cell”) (arrow) **D.** Smear from the same patient showing intense myeloperoxidase staining (O-toluidine stain against Giemsa stain background).

Figure 2.

Kaplan-Meier event-free and overall survival curves in the **AIDA0493 trial** ($n = 107$), the largest paediatric series reported during the all-*trans* retinoic acid era. This research was originally published in *Blood*. Testi, A.M., Biondi, A., Lo Coco, F., Moleti, M.L., Giona, F., Vignetti, M., Menna, G., Locatelli, F., Pession, A., Barisone, E., De Rossi, G., Diverio, D., Micalizzi, C., Aricò, M., Basso, G., Foa, R., Mandelli, F. GIMEMA-AIEOP AIDA protocol for the treatment of newly diagnosed acute promyelocytic leukaemia (APL) in children. *Blood*. 2005;**106**:447-453. © the American Society of Hematology

Table I**Suggested guidelines for initial management of childhood APL**

•	Begin ATRA at first suspicion of APL, rather than waiting for molecular confirmation.
•	Monitor CBC and coagulation values 3–4 times daily, administering platelets and fresh frozen plasma as needed to maintain platelet count $> 30\text{--}50 \times 10^9/\text{l}$ and fibrinogen $> 1.5 \text{ g/l}$. The benefit of heparin and tranexamic acid is unproven.
•	Administer dexamethasone to patients with presenting WBC count $> 10 \times 10^9/\text{l}$ and to those with standard-risk APL who develop leucocytosis (WBC $> 10 \times 10^9/\text{l}$) during induction therapy.
•	Avoid leukapheresis to avert the risk of catastrophic bleeding.
•	Avoid lumbar puncture during induction therapy and before DIC has resolved.
•	Avoid placement of indwelling central venous catheters during early induction.
•	Be vigilant for signs of APL differentiation syndrome. If present, discontinue ATRA or ATO and administer IV dexamethasone [*] until complete resolution of signs and symptoms. At that time, resume ATRA or ATO at 75% [†] or 50% [‡] of initial dose.
•	Avoid myeloid growth factors during induction therapy.
•	Avoid bone marrow aspiration/biopsy at the peripheral cell nadir during induction; morphological and molecular findings at this time are clinically irrelevant.
•	Avoid azole antifungals during ATRA therapy, as they increase the risk of ATRA toxicity [¥]
•	Monitor the QTc interval frequently during ATO treatment and avoid other drugs that may prolong the QTc interval.

APL, acute promyelocytic leukaemia; ATRA, all-*trans* retinoic acid; CBC, complete blood count; DIC, disseminated intravascular coagulation; WBC, white blood cell count; ATO, arsenic trioxide

^{*} No dose has been established, but doses of $5 \text{ mg/m}^2 \text{ bid}$ (ICC-APL 01) and 0.25 mg/kg bid (COG-AAML0631) have been reported.

[†] COG-AAML0631

[‡] ICC-APL 01

[¥] Yarali *et al.*, (2008)

Table II

Prognostic factors in acute promyelocytic leukaemia

Prognostic Factors*	Remarks
Predictors of relapse	
Positive <i>PML-RARA</i> at end of consolidation [†]	Most important predictor of relapse Identifies relapse-risk categories for adapted therapy
Initial white blood cell and platelet counts [‡]	
<ul style="list-style-type: none">Low risk: WBC 10 × 10⁹/l, platelets >40 × 10⁹/lIntermediate risk: WBC 10 × 10⁹/l, platelets 40 × 10⁹/lHigh risk: WBC >10 × 10⁹/l	
High body mass index [§]	
Predictors of early death	
Initial WBC > 10 × 10 ⁹ /l [¥]	Most important predictor of early death Predictors of early haemorrhagic death
Coagulopathy, high creatinine, high peripheral blast cell count [£]	
Suspected but unproven prognostic factors	
<i>FLT3</i> abnormalities [€]	OS higher in <i>FLT3</i> -ITD–negative patients <i>FLT3</i> mutations associated with higher risk of induction death Higher relapse rate and lower OS in <i>FLT3</i> -ITD-positive patients (in univariate analysis only) on PETHEMA protocols
M3v subtype [¶]	Greater risk of early death on non-ATRA regimens In ATRA era, not prognostic after adjustment for WBC
BCR3-isoform of <i>PML-RARA</i> [#]	Associated with higher relapse rate
CD56 expression ^{\$}	Associated with higher relapse rate

PML-RARA, promyelocytic leukaemia protein-retinoic acid receptor-alpha; WBC, white blood cell count; AIDA, Italian ATRA/Idarubicin protocol; *FLT3*-ITD, *FLT3*-internal tandem duplication; OS, overall survival; M3v, microgranular variant; ATRA, all-*trans*retinoic acid; PETHEMA, Programa para el Estudio y Tratamiento de las Hemopatías Maligna.

* Overall prognostic factors in children and adults with APL

[†] Diverio *et al.* (1998); Suzuki *et al.* (2001)

[‡] Sanz *et al.* (2000)

[§] Breccia *et al.* (2012)

[¥] Testi *et al.* (2005); Bally *et al.* (2012); Burnett *et al.* (1999)

[£] de la Serna *et al.* (2008)

[€] Arrigoni *et al.* (2003), Kutny *et al.* (2012), Gale *et al.* (2005), & Barragan *et al.* (2011)

[¶] Bassan *et al.* (1995); Tallman *et al.* (2010)

[#] Albitar *et al.* (1999); Gallagher *et al.* (1997)

^{\$} Ferrara *et al.* (2000).

Table III

Results of recent adult APL trials using ATRA plus chemotherapy

Group (reference)	Strategy	Outcome	Conclusions
PETHEMA LPA 2005 (Sanz <i>et al</i> , 2010)	<ul style="list-style-type: none"> • ATRA+IDA • Low/intermediate risk: lower Mitox dose • High risk: HD-Ara-C in consolidation 	All patients: 3-year DFS: 92% 3-year OS: 89% High-risk: 3-year DFS: 82% 3-year CIR: 11%	Low/intermediate risk: less myelosuppression & comparable survival HD-Ara-C: lower CIR than LPA99 in high-risk APL
European APL93 (Adès <i>et al</i> , 2010)	<ul style="list-style-type: none"> • Randomized induction: ATRA+CT vs ATRA→CT • Randomized maintenance: ATRA/MP/MTX vs observation 	10-year EFS: 76% ATRA+CT vs 64% ATRA→CT 10-year CIR: 13% maintenance vs 43% observation	ATRA+CT induction more effective than ATRA→CT. ATRA/MP/MTX maintenance better for patients with initial WBC > 5
European APL2000 (Adès <i>et al</i> , 2006)	<ul style="list-style-type: none"> • Induction: ATRA+Dauno+Ara-C • Consolidation: <ul style="list-style-type: none"> – WBC 10: randomized to ATRA+Dauno ± Ara-C – WBC > 10: + HD-Ara-C 	WBC 10: 2-year EFS 93% in Ara-C arm vs 77% 2-year CIR: 5% vs 16% WBC > 10: 2-year EFS 89% 2-year CIR 3%	HD-Ara-C in consolidation reduced relapse risk in high-risk APL.
GIMEMA AIDA0493 (Avvisati <i>et al</i> , 2011)	<ul style="list-style-type: none"> • Induction: ATRA+IDA • Consolidation: IDA/Ara-C/TG, Mitox/VP16 • Maintenance: <i>PML-RARA</i>-neg. randomized to MP/MTX vs ATRA vs MP/MTX/ATRA vs observation 	12-year DFS very similar in 4 maintenance arms: 68–70%	No long-term benefit from maintenance if <i>PML-RARA</i> -neg. at end of consolidation.
AIDA2000 (Lo Coco <i>et al</i> , 2010)	<ul style="list-style-type: none"> • Addition of ATRA in consolidation • High-risk: ARA-C/VP16/TG in consolidation 	All patients: 6-year DFS: 86% 6-year CIR: 11% High-risk: 6-year DFS: 84%, 6-year CIR: 9%	Lower CIR than AIDA0493. Consolidation with ATRA improved outcome. Ara-C in consolidation important in high-risk APL.
North American Intergroup-C9710 (Powell <i>et al</i> , 2010)	<ul style="list-style-type: none"> • ATRA+Dauno+Ara-C • Consolidation: randomized to ATRA+Dauno ± ATO • Maintenance: Randomized to ATRA/MP/MTX vs ATRA for 1 year 	3-year EFS: 80% in ATO arm vs 63% standard arm 3-year OS: 86% in ATO arm vs 81% standard arm	Consolidation with ATO after ATRA + anthracycline induction improved EFS.

PETHEMA, Programa para el Estudio y Tratamiento de las Hemopatías Maligna; GIMEMA, Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto; CT chemotherapy; IDA, idarubicin; ATRA, all-*trans* retinoic acid; ATO, arsenic trioxide; Mitox, mitoxantrone; Ara-C, cytarabine; HD, high dose; Dauno, daunorubicin; VP16, etoposide; TG, thioguanine; CIR, cumulative incidence of relapse; MP, mercaptopurine; MTX, methotrexate; DFS, disease-free survival; EFS, event-free survival; OS, overall survival; WBC, white blood cell count $\times 10^9/l$.

Table IV

Results of recent clinical trials for paediatric APL

Study, period (reference)	No. of Patients	Median Age (years)	CR rate (%)	Outcome	Conclusions
European APL, 1993-2004 (Bally <i>et al.</i> , 2012)	58 Adolescents 26 Children	16.5 6	100% 92%	5-year OS: 93% 5-year OS: 80%	Children < 4years experienced more frequent relapse and a higher toxicity rate.
BFM, 1993-2004 (Creutzig <i>et al.</i> , 2010)	81	-	93%	5-year OS: 89% 5-year EFS: 73%	High cure rates can be achieved with lower cumulative anthracycline dose.
North American Intergroup Trial INT0129, 1992-1995 (Gregory <i>et al.</i> , 2009)	53	12	81%	5-year OS: 69% 5-year EFS: 41%	Better DFS in children who received ATRA in induction and maintenance.
PETHEMA 1996-2004 (Ortega <i>et al.</i> , 2005)	66	12	92%	5-year OS: 87% 5-year EFS: 77%	Higher incidence of hyperleucocytosis in children than adults; higher relapse rate in children with hyperleucocytosis.
GIMEMA-AIEOP 1993-2000 (Testi <i>et al.</i> , 2005)	124	11.6	96%	10-year OS: 89% 10-year EFS: 76%	Better molecular DFS with ATRA and chemotherapy vs. ATRA alone in maintenance.
Chinese Study 2002-2007 (Zhou <i>et al.</i> , 2010)	19	10	89%	5-year OS: 84% 5-year EFS: 73%	Single-agent ATO is highly effective during induction and postremission.
Chinese Study 1999-2005 (Zhang <i>et al.</i> , 2008)	65	13	91%	5-year OS: 89% 5-year EFS: 78%	ATRA and ATO combination is effective and safe.
Indian Study 1998-2003 (George <i>et al.</i> , 2004)	11	13	91%	3-year OS: 91% 3-year RFS: 81%	ATO can induce molecular CR in most children with minimal toxicity.

APL, acute promyelocytic leukaemia; BFM, Berlin-Frankfurt-Münster; INTO, ; PETHEMA, Programa para el Estudio y Tratamiento de las Hemopatías Malignas; GIMEMA, Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto; AIEOP, Associazione Italiana di Ematologia e Oncologia Pediatrica; ATRA, all-*trans* retinoic acid; ATO, arsenic trioxide; CR, complete remission; EFS, event-free survival; DFS, disease-free survival; OS, overall survival.