AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Evidence Status Report: arsenic trioxide (TRISENOX®) in combination with all-trans retinoic acid for the first-line treatment of acute promyelocytic leukaemia in adult patients unsuitable for anthracycline-based therapy

August 2016

KEY FINDINGS

Report background

Acute promyelocytic leukaemia (APL) is a distinct subtype of acute myeloid leukaemia and presents clinically with coagulation disorders, which are associated with life-threatening haemorrhages. All-trans retinoic acid (ATRA) in combination with anthracycline-based chemotherapy is the mainstay treatment for APL in patients deemed suitable for intensive therapy. For patients unsuitable for anthracycline-based therapy, arsenic trioxide (ATO) in combination with ATRA may offer a treatment option. ATO is licensed for induction of remission and consolidation in adult patients with relapsed/refractory APL, however, ATO is not licensed for the first-line treatment of this indication and therefore its use is off-label. A cohort of patients has been identified through data from individual patient funding request (IPFR) panels; based on unmet need within the service this medicine was considered to be suitable for assessment via the One Wales process.

Efficacy/Effectiveness

Published results from two phase III trials demonstrates that ATRA plus ATO is at least not inferior and may be superior to ATRA plus chemotherapy in the treatment of patients with APL; no significant difference in the quality of life was reported. These trials were analysed in a meta-analysis together with a third trial. The results of which support the trial findings.

Safety

No new safety signals have been observed for ATO in combination with ATRA for the first-line treatment of APL in patients unsuitable for anthracycline-based therapy.

Patient factors

ATO should only be considered for patients deemed unsuitable for anthracycline-based therapy due to frailty or co-morbidities.

Cost effectiveness

One study was identified assessing the cost-effectiveness of ATRA plus ATO versus ATRA plus idarubicin and ATRA plus cytarabine and chemotherapy from a US payer perspective. Cost effectiveness estimates have been calculated by the All Wales Therapeutics and Toxicology Centre (AWTTC) but are subject to large uncertainty due to the assumptions made in calculating these estimates. With this caveat, the estimated incremental cost-effectiveness ratio per quality-adjusted life-year gained was £3,669 versus ATRA plus idarubicin and £3,368 versus ATRA plus cytarabine and chemotherapy.

Budget impact

The addition of ATO to ATRA for the first line treatment of APL in patients unable to receive chemotherapy is likely to result in an additional cost of £185,645 per annum. This is based on five patients being eligible for treatment in Wales each year.

Impact on health and social care services

Minimal increased use of existing services.

Innovation and/or advantages

Arsenic trioxide offers a treatment choice for APL in patients unsuitable for anthracycline-based therapy.

BACKGROUND

Target group

The indication under consideration is arsenic trioxide (ATO) in combination with all-trans retinoic acid (ATRA) for the first-line treatment of acute promyelocytic leukaemia (APL), characterised by the presence of the t(15;17) translocation and/or the presence of the Pro-Myelocytic Leukaemia/Retinoic-Acid-Receptor-alpha (PML-RARA) gene, in adult patients unsuitable for anthracycline-based therapy.

Technology

ATO binds specifically to the PML moiety of the disease specific PML-RARA oncoprotein, leading to its degradation and resulting in partial differentiation and induction of apoptosis of leukemic promyelocytes[1].

Marketing authorisation date: Not applicable, off-label

ATO in combination with ATRA for the first-line treatment of APL in adult patients unsuitable for anthracycline-based therapy is off-label.

ATO received market authorisation in 2002 for the induction of remission and consolidation in adult patients with relapsed/refractory APL, characterised by the presence of the t(15;17) translocation and/or the presence of the PML-RARA gene[2].

Dosing

According to the Summary of Product Characteristics (SPC), ATO is administered intravenously at a fixed dose of 0.15 mg/kg/day given daily until bone marrow remission is achieved (less than 5% blasts present in cellular bone marrow with no evidence of leukaemic cells)[2]. If bone marrow remission has not occurred by day 50, dosing is discontinued. Consolidation treatment begins 3 to 4 weeks after completion of induction therapy. ATO is administered intravenously at a dose of 0.15 mg/kg/day for 25 doses given 5 days per week, followed by 2 days interruption, repeated for 5 weeks[2]. ATRA is administered at a dose of 45mg/m^2 daily in divided doses for up to 90 days[3].

Clinical experts have indicated that in practice, the ATO regimen is loosely based on the AML17 regimen and is most often used as an eight-week induction consisting of 0.3 mg/kg daily for five days followed by 0.25 mg/kg twice weekly for seven weeks, followed by four courses of consolidation therapy with each course consisting of daily ATO at a dose of 0.3 mg/kg daily for five days followed by 0.25 mg/kg twice weekly for three weeks. In AML17 the ATRA regimen was ATRA daily (45 mg/m^2) until remission or until day 60, and then in a two weeks on and two weeks off schedule. This regimen has been used in the budget impact assessment.

Clinical background

APL is a distinct subtype of acute myeloid leukaemia (AML), characterised by chromosomal translocation t(15;17) generating fusion of PML and RARA genes[4]. This fusion yields an aberrant, oncogenic protein (PML-RARA) which disturbs the cellular signalling of wild-type RARA in myeloid progenitor cells and consequently blocks myeloid differentiation at the promyelocyte stage. Clinically, APL presents with coagulation disorders, which are associated with life-threatening haemorrhages[4].

The introduction of ATRA in the 1980s, in combination with chemotherapy, revolutionised the treatment of APL and transformed it from the most fatal into the most highly curable acute leukaemia[5]. Multicenter trials examining the efficacy of ATRA in combination with anthracycline-based chemotherapy have reported remission rates of up to 95% and cure rates exceeding 80%[1].

Incidence/prevalence

In Wales in 2014, there were 178 new cases of AML diagnosed and 128 deaths[6]. APL accounts for approximately 5–10% of AML cases[4], which equates to approximately 9–18 of the AML cases diagnosed in Wales in 2014. Clinical experts indicate that five patients in Wales per year are likely to be unsuitable for anthracycline-based therapy and therefore eligible for ATO treatment. In the UK between 2002 and 2013, AML age-standardised incidence rates increased by 7%, this includes an increase in males (8%) and stable rates in females[7].

Current treatment options

The combination of ATRA plus chemotherapy is currently considered the standard of care for newly diagnosed APL[8]. Patients with PML-RARA positive APL, deemed suitable for intensive therapy are treated with concurrent ATRA and anthracycline-based chemotherapy for induction, followed by anthracycline-based consolidation therapy[9]. For relapsed disease, ATRA should not be used as a single agent therapy due to the significant possibility of acquired secondary resistance and ATO should only be used in patients with confirmed PML-RARA positive APL[9]. According to the 2009 European LeukaemiaNet recommendations of an expert panel, the use of ATO-based regimens should be restricted to patients included in clinical trials or for those in whom chemotherapy (especially anthracyclines) is contraindicated[8]. For those patients who are unsuitable for intensive chemotherapy, clinical experts indicate that without the availability of ATO patients would enter palliative care, consisting of treatment with ATRA and low dose chemotherapy such as hydroxycarbamide and low dose cytarabine.

Guidance and related advice

- NHS Wales, South Wales Cancer Network: Acute Myeloid Leukaemia Haematological Pathway (2015)[10]
- *Blood:* Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet (2009)[8]
- *British Journal of Haematology*: Guidelines on the management of acute myeloid leukaemia in adults (2006)[9]

SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

A comprehensive literature search conducted by the All Wales Therapeutics and Toxicology Centre (AWTTC) identified two phase III studies investigating the efficacy and safety of ATRA plus ATO compared to ATRA plus chemotherapy for the treatment of APL. These studies were also identified within a meta-analysis comparing the efficacy of ATRA plus ATO with ATRA plus chemotherapy in patients with APL. The studies are briefly described below.

Efficacy

Retinoic acid and arsenic trioxide for acute promyelocytic leukemia (APL0406)
This was a phase III, randomised, open-label, multicentre trial comparing ATRA plus ATO with ATRA plus chemotherapy in patients with newly diagnosed APL[1]. The study was designed as a non-inferiority trial to show that the difference between the rates of event-free survival (EFS) at two years in the two groups was not greater than 5%[1].

Patients (n = 156) aged between 18 to 71 years with newly diagnosed APL, classified as low-to-intermediate risk (white cell count ≤ $10x10^9$ per litre), were randomised to receive ATRA plus ATO (n = 77) or ATRA plus chemotherapy (n = 79)[1]. Patients in the former arm received ATRA (45 mg/m^2) plus ATO (0.15 mg/kg) daily until complete remission or for a maximum of 60 days, followed by four courses of ATO five days per week, in a four weeks on and four weeks off schedule, and ATRA two weeks on and two weeks off for a total of seven courses. In the ATRA plus chemotherapy group, patients received idarubicin (12 mg/m^2) on days two, four, six and eight plus ATRA (45 mg/m^2) daily until complete remission or for a maximum of 60 days, followed by consolidation therapy with ATRA plus chemotherapy and maintenance therapy with low dose chemotherapy and ATRA. There were no significant differences in the baseline characteristics between the two study groups[1].

The primary end point was EFS at two years after diagnosis, with treatment failure defined as any of the following: no achievement of haematological complete remission after induction therapy, no achievement of molecular complete remission after three consolidation courses, molecular relapse, haematological relapse, or death[1].

Of the 156 patients in the intention-to-treat population, 6 (4%) could not be evaluated at 24 months for the primary analysis because a molecular evaluation was not performed or follow-up was insufficient. Of the remaining 150 patients, 97% (72 of 74 patients) in the ATRA and ATO group and 86% (65 of 76 patients) in the ATRA plus chemotherapy group were alive and free of events at two years ($p < 0.001$ for non-inferiority and $p = 0.02$ for superiority of ATRA plus ATO). Haematological complete remission was achieved in all 77 patients (100%) in the ATRA plus ATO group and in 75 of 79 patients (95%) in the ATRA plus chemotherapy group ($p = 0.12$). The two-year overall survival probability was 99% (95% confidence interval [CI] 96–100) in the ATRA and ATO group and 91% (95% CI 85–97) in the ATRA plus chemotherapy group ($p = 0.02$)[1].

Arsenic trioxide and all-trans retinoic acid treatment for acute promyelocytic leukaemia in all risk groups (AML17): results of a randomised, controlled phase 3 trial
This was a phase III, randomised, controlled, multicentre trial comparing ATRA and ATO treatment regimen with the standard chemotherapy-based regimen (ATRA and idarubicin) in both high-risk and low-risk patients with APL[11]. AML17 is an open label trial for patients with AML and high-risk myelodysplastic syndrome including APL; this paper reports on the APL arm only.

Patients (n = 235) aged ≥ 16 years with APL were randomised 1:1 to receive treatment with ATRA and ATO (n = 116) or ATRA and idarubicin (n = 119)[11]. Of these 235 participants, 57 were high-risk patients (30 in the ATRA and ATO group and 27 in the ATRA and idarubicin group). Patients in both groups received ATRA daily (45 mg/m^2) until remission or until day 60, and then in a two weeks on and two weeks off schedule. In the ATRA and ATO group, patients received five courses of treatment: ATO was given intravenously at a dose of 0.3 mg/kg on days one to five of each course, and then in weeks two to eight of course one and weeks two to four of courses two to five at 0.25 mg/kg twice weekly. In the ATRA and idarubicin group, patients received four courses of treatment: idarubicin was given intravenously at a dose of 12 mg/m^2 on days two, four, six and eight of course one and 5 mg/m^2 on days one to four of course two; mitoxantrone 10 mg/m^2 on days one to four of

course three; and idarubicin 12 mg/m^2 on day one of course four. In the ATRA and ATO groups, 28 of the 30 high-risk patients received gemtuzumab ozogamicin and two received an anthracycline, with a further seven low-risk patients given gemtuzumab ozogamicin for a rising white blood cell count. The median age of the participants was 47 years. The baseline characteristics were similar between both groups[11].

The primary outcome was quality of life, assessed with the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire and the Hospital Anxiety and Depression Scale[11]. Questionnaires were completed at baseline and at 3, 6, 12 and 24 months post randomisation[11].

The results showed no statistically significant difference in the primary quality of life outcome, global functioning, between the two groups (effect size 2.17; 95% CI −2.79 to 7.12; p = 0.39)[11]. On other measures, point estimates tended to favour ATRA and ATO over ATRA and idarubicin, with significant benefits recorded for cognitive and role functioning, although the size of any benefit was modest. The authors highlight that reduced infusions with ATRA and ATO treatment compared to ATRA and idarubicin would likely be beneficial; however the quality of life surveys used in this study did not directly capture this parameter[11]. Table 1 shows the results of the secondary endpoints.

Table 1. Secondary endpoints from the AML17 study[11]

Outcome	ATRA and idarubicin (n = 119)	ATRA and ATO (n = 116)	OR/HR (95% CI)
Complete remission	106 (89%)	109 (94%)	OR 0.54 (0.21–1.34) p = 0.18
Four-year survival	89%	93%	HR 0.60 (0.26–1.42) p = 0.25
Four-year event-free survival	70%	91%	HR 0.35 (0.18–0.68) p = 0.002
Four-year cumulative incidence of morphological relapse	18%	1%	HR 0.16 (0.06–0.46) p = 0.0007
Four-year cumulative incidence of molecular relapse*	27%	0%	HR 0.12 (0.05–0.30) p < 0.0001
ATRA: all-trans retinoic acid; ATO: arsenic trioxide; OR: odds ratio; HR: hazard ratio; CI: confidence interval. * In patients achieving molecular negativity.			

ATRA plus ATO versus ATRA plus chemotherapy for newly diagnosed APL: a meta-analysis

This meta-analysis aimed to comparatively evaluate the efficacy of ATRA plus ATO and ATRA plus chemotherapy in newly diagnosed adult APL patients[12]. Three trials involving 585 patients were identified for inclusion in the meta-analysis, including the APL0406 and AML17 discussed above. The third trial (APML4) was an Australasian, prospective multicentre trial. This trial was less relevant since ATRA and ATO therapy was combined with idarubicin during induction, followed by consolidation with ATO plus ATRA without chemotherapy. The cumulative ATO doses in the three trials were 16.8, 17.0 and 12.2 mg/kg in APL0406, AML17 and APML4, respectively. The median follow-up time was 30.5–50.4 months in the three trials[12].

A fixed effects model was used as there was no statistical heterogeneity among the trials[12]. The results are shown in Table 2.

Table 2. Results from the meta-analysis[12]

Outcome	ATRA + ATO ± chemotherapy	ATRA + chemotherapy	RR/HR (95% CI)
Complete remission	304 (95.9%)	245 (91.4%)	RR 1.05 (1.01–1.10) p = 0.03
Relapse rate	8 (2.7%)	36 (14.5%)	RR 0.17 (0.08–0.37) p < 0.00001
Relapse-free survival*	NR	NR	HR 0.23 (0.07–0.77) p = 0.02
Event-free survival†	NR	NR	HR 0.38 (0.22–0.67) p = 0.009
Overall survival	NR	NR	HR 0.44 (0.24–0.82) p = 0.009

ATRA: all trans retinoic acid; ATO: arsenic trioxide; RR: risk ratio; HR: hazard ratio; CI: confidence interval; NR: not reported.
*Evaluated in studies AML17 and APML4
†Evaluated in studies APL0406 and APML4

Safety

The Summary of Product Characteristics (SPC) lists adverse events (AEs) that may be associated with ATO treatment[2]. Serious AEs associated with ATO include APL differentiation syndrome and prolongation of the QT interval[2]. Thirteen percent of patients may develop hypokalaemia or hyperglycaemia[8]. APL differentiation syndrome is a relatively common and potentially severe complication seen in patients treated with ATRA and/or ATO and is characterised by fever, dyspnoea, weight gain, pulmonary infiltrate and pleural or pericardial effusions, with or without leukocytosis[13]. Patients require prompt treatment with dexamethasone. Temporary discontinuation of ATRA and ATO is indicated only in severe cases (i.e. patients developing renal failure or requiring admission to the intensive care unit due to respiratory distress)[8].

In the APL0406 study grade three or four neutropenia and thrombocytopenia lasting more than 15 days were significantly ($p \leq 0.02$) more frequent both during induction therapy and after each consolidation course in the ATRA plus chemotherapy group than in the ATRA and ATO group[1]. A total of 43 of 68 (63%) patients in the ATRA and ATO group and 4 of 69 patients (6%) in the ATRA plus chemotherapy group had grade three or four hepatic toxic effects during induction or consolidation therapy (for patients in both groups) or during maintenance therapy (for patients in the ATRA plus chemotherapy group) ($p < 0.001$). In all cases, the toxic effects were resolved with temporary discontinuation of treatment. Prolongation of the corrected QT interval was reported in 12 patients (16%) in the ATRA and ATO group and in no patients in the ATRA plus chemotherapy group ($p < 0.001$)[1]. This led to permanent discontinuation of therapy for one ATO-treated patient.

In the AML17 study 146 serious AEs (64 in the ATRA and ATO group versus 82 in the ATRA and idarubicin group) were recorded in 99 patients (46 versus 53 in the two groups, respectively)[11]. During treatment courses one to two, grade III to IV toxicities were reported in 40 patients in the ATRA and ATO group and 57 patients in the ATRA and idarubicin group. For treatment course one, alopecia, gastrointestinal events, hyperbilirubinaemia, and cardiac events were more common with ATRA and idarubicin. After course one of treatment, liver grade III to IV toxicities of alanine transaminase were more frequent in the ATRA and ATO group than in the ATRA and idarubicin group. Liver toxicities did not differ between the groups after treatment course two. After course two, cardiac toxicity was more common in the ATRA and ATO group than in the ATRA and idarubicin group ($p = 0.001$). Supportive care requirements, including hospital stay, units of blood, units of platelets and intravenous antibiotics, were significantly lower ($p \leq 0.0001$) during the first two courses of treatment with ATRA and ATO than ATRA and idarubicin on all measures except for antibiotic use in course two. Compared with ATRA and idarubicin, ATRA and ATO treatment was associated with an

average of 7.4 fewer days in hospital, 4.5 fewer units of blood, 4.3 fewer units of platelets and 10.7 fewer days of antibiotics[11].

Clinical effectiveness issues

The phase III, randomised, open-label APL0406 study concluded that ATRA plus ATO is at least not inferior and may be superior to ATRA plus chemotherapy in the treatment of patients with low-to-intermediate-risk APL[1]. A limitation of this study was its open-label design[1].

In the randomised, controlled, open-label AML17 trial, AML patients recruited from 81 hospitals, including the UK, were treated with either ATRA and ATO or ATRA and idarubicin[11]. The study population consisted of low-to-intermediate-risk and high-risk patients. In the ATRA and ATO group the latter population were also treated with gemtuzumab ozogamicin or an athracycline. The p values were not reported for AEs between both treatment groups. The authors report that the attenuated dosing schedule of ATO used in this trial offers the obvious advantage of convenience for the patients compared with ATRA and idarubicin, but also reduces administration and acquisition costs of ATO[11].

The meta-analysis compared the efficacy of ATRA plus ATO with ATRA plus chemotherapy for adult patients with newly diagnosed APL[12]. Results from the analysis concluded that ATRA plus ATO may be preferred to standard ATRA plus chemotherapy protocol, particularly in low-to-intermediate risk APL patients[12]. However, there is limited evidence for its use long term and in high risk APL patients.

There were several limitations of the meta-analysis as reported by the authors[12]. Firstly, a small number of studies were included and one of them was a non-randomised trial. Additionally, no trial reported blinding of participants, personnel or the progress of outcome assessment. There was heterogeneity in the types of ATRA plus ATO regimens administered among the trials and the optimal doses and scheme for ATO in APL treatment remains uncertain. The AEs were recorded inconsistently among the three trials, but all studies suggested an acceptable toxicity profile of ATRA plus ATO therapy[12].

These studies did not include patients unsuitable for anthracycline-based therapy, representative of the indication. The clinical effectiveness of ATO plus ATRA and the associated AEs have not been investigated in this fragile population.

SUMMARY OF EVIDENCE ON COST-EFFECTIVENESS

Cost-effectiveness evidence

Literature searches by AWTTC identified one relevant cost-effectiveness study. This study assessed the cost-effectiveness of ATO plus ATRA (induction and consolidation with ATO and ATRA; no maintenance) versus ATRA plus idarubicin (induction and consolidation with ATRA and idarubicin, plus mitoxantrone in consolidation, and maintenance with 6-mercaptopurine plus methotrexate and ATRA) and ATRA plus cytarabine and additional chemotherapy (induction with ATRA, cytarabine and daunorubicin, consolidation with ATRA and daunorubicin, and maintenance with 6-mercaptopurine, methotrexate and ATRA) when used in the first-line treatment of newly diagnosed low-to-intermediate-risk APL patients[14]. The methodology for this study is described below. The model included costs associated with the medicine intervention, administration and monitoring costs and costs associated with AEs. These costs were reported in US dollars and therefore were converted to British pounds using the average exchange rate for 2015. We have extrapolated the data for quality-adjusted life-years (QALYs) from this study, together with UK costs to provide an estimate incremental cost-effectiveness ratio (ICER) for NHS Wales.

A lifetime horizon Markov cohort model was used to estimate the cost-effectiveness of first-line treatment regimens for patients with APL from a United States third party payer perspective[14]. Patients enter the model in the first-line stable disease health state. During each cycle, patients can remain in this state or progress to the second-line stable/first-line disease event state. Patients who experienced a disease event following first-line treatment were treated with second-line ATO. Patients could remain in this state or move to the disease event state after second-line treatment. Patients whose disease progressed following first- and second-line treatments were assumed to enter a clinical trial. Patients could die from any state as a result of the effects of the disease, treatment-related mortality or natural causes. The majority of base-case parameters used within the model were estimated from published literature and other secondary sources[14].

Patients started in the model at 45 years of age and analysis continued until 100 years of age or death[14]. Both outputs and cost inputs were discounted at a rate of 3% per year after the first year in the model. The main clinical parameters included in the model were EFS and overall survival. Kaplan-Meier curves were obtained from published clinical trials for each of the comparators in the first-line and second-line settings. Due to distinct differences in the probabilities of the Kaplan-Meier curves in the second-line setting for the first two years of treatment compared to treatment after two years, two sets of transition probabilities were estimated for the second-line treatment Markov states. It was assumed that the second set of transition probabilities came into effect at month 24. Monthly estimates of EFS and overall survival were extrapolated from Kaplan-Meier curves and used to estimate the monthly transition probabilities between each health state of the Markov model[14].

The probabilities of AEs in each treatment phase of first-line therapy were derived from published clinical trials of the comparators, with particular focus on serious AEs[14]. However, there were no AEs reported for the ATRA plus idarubicin and additional chemotherapy regimen and consequently the AE rates were set to zero, thus increasing the potential for bias. Similarly, in the second-line setting AEs were not reported in the published clinical trials[14].

Utility values were derived from published studies in chronic lymphocytic leukemia (CLL) because utilities were not available for APL disease[14]. Age-adjusted utilities were calculated to address the limitation of CLL utilities since such patients are usually older and have worse outcomes than APL patients. The utilities were also adjusted for the United States population. The utility estimates for each health state were: first-line stable disease = 0.78, first-line event/second-line stable disease = 0.65 and second-line disease event = 0.47. Patients were assumed to receive the treatment regimes as outlined in the APL0406[1] and C9710[15] clinical trials. The model outputs, including life years and QALY from the United States population, for the first-line treatment of APL were used together with the total costs converted to British pounds to estimate ICERs per QALY gained as detailed in Table 3[3,14]. The cost-effectiveness calculations should be interpreted with caution and there are several caveats which must be considered. The medicine acquisition costs, as well as the resources used and the pattern of care were assumed to be comparable between the US and Wales.

Table 3. Results of the base case analysis.

	ATO + ATRA	Comparator treatment	Difference
ATO + ATRA versus ATRA + IDA			
Total costs	£89,087	£66,337	**£22,750**
Total QALYs	14.33	8.13	**6.2**
ICER	**£3,669**		
ATO + ATRA versus ATRA + AraC + additional chemotherapy			
Total costs	£89,087	£63,421	**£25,666**
Total QALYs	14.33	6.71	**7.62**
ICER	**£3,368**		

ATO: arsenic trioxide; ATRA: all-trans retinoic acid; ICER: incremental cost effectiveness ratio; IDA: idarubicin; AraC: cytarabine; QALY: quality-adjusted life-year.

BUDGET IMPACT

The list price of ATO (10 mg/10 ml concentrate solution for infusion) is £2,920 and list price of ATRA is £233.30 (100 x 10 mg capsule)[3]. Table 4 details the estimate for the annual budget impact in Wales. This excludes VAT and any local contracting agreements. The following assumes an average weight of 63 kg and a body surface area of 1.73 m^2. Clinical experts have highlighted that the ATRA plus ATO regimen used in the AML17 study is used clinically in Wales. Therefore, the budget impact has been estimated for this regimen. Additionally, clinical experts have suggested that the comparator, and therefore the displaced medicine, would be palliation therapy with ATRA plus low dose hydroxycarbamide and cytarabine. However, the dose and the duration of treatment are determined for each patient on an individual basis; for the purposes of this report an example regimen has been used based on clinical expert advice (see table below).

Table 4. Projected Budget Impact in Wales

	Year 1	Year 2	Data Source
Arsenic trioxide* + ATRA*	£38,864	£38,864	MIMS[3]
Number of patients newly treated per annum	5	5	Clinical expert
Net medicine cost	**£194,320**	**£194,320**	
Medicine expenditure of the displaced medicine*†	£8,675	£8,675	MIMS[3]
Net financial cost	**£185,645**	**£185,645**	

* This assumes vial wastage.
† ATRA (45 mg/m^2 daily) for 90 days, hydroxycarbamide (2 g daily) for 90 days and cytarabine (20 mg twice daily) for 10 days.

Budget impact issues

- The budget impact has not considered the discontinuation of therapy and mortality rates.
- The budget impact is based on drug acquisition costs only and therefore does not consider administration and monitoring costs, hospitalisation costs, adverse event costs or any additional palliation costs.

ADDITIONAL FACTORS

Prescribing unlicensed medicines

ATO is not licensed to treat this indication and is therefore 'off label'. Providers should consult the General Medical Council Guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

REFERENCES

1. Lo-Coco F, Avvisati G, Vignetti M et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. *The New England Journal of Medicine.* 2013;369(2):111-121. Available at: http://www.nejm.org/doi/full/10.1056/NEJMoa1300874#t=article. Accessed August 2016.
2. Teva Pharma B.V. TRISENOX®. Summary of Product Characteristics. Feb 2015. Available at: https://www.medicines.org.uk/emc/medicine/28860. Accessed August 2016.
3. Haymarket Publications. Monthly Index of Medical Specialities (MIMS). Available at: http://www.mims.co.uk/. Accessed August 2016.
4. Lengfelder E, Hofmann W, and Nowak D. Impact of arsenic trioxide in the treatment of acute promyelocytic leukemia. *Leukemia.* 2012;26:433-442. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21904379. Accessed August 2016.
5. Wang Z, and Chen Z. Acute promyelocytic leukemia: from highly fatal to highly curable. *Blood.* 2008;111:2505-2515. Available at: http://www.bloodjournal.org/content/111/5/2505.long?sso-checked=true. Accessed August 2016.
6. Welsh Cancer Intelligence and Surveillance Unit. Interactive cancer statistics tool. Feb 2016. Available at: http://www.wcisu.wales.nhs.uk/interactive-cancer-statistics-tool. Accessed August 2016.
7. Cancer Research UK. Acute myeloid leukaemia (AML) incidence statistics. 2013. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-aml/incidence#heading-Two. Accessed August 2016.
8. Sanz M, Grimwade D, Tallman M et al. Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. *Blood.* 2009;113(9):1875-1891. Available at: http://www.bloodjournal.org/content/113/9/1875.long?sso-checked=true. Accessed August 2016.
9. Milligan D, Grimwade D, Cullis J et al. Guidelines on the management of acute myeloid leukaemia in adults. *British Journal of Haematology.* 2006;135(4):450-474. Available at: http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2006.06314.x/pdf. Accessed August 2016.
10. NHS Wales SWCN. Acute Myeloid Leukaemia Haematological Pathway. March 2015. Available at: http://www.cancerservicesdirectory.wales.nhs.uk/document/266965/. Accessed August 2016.
11. Burnett A, Russell N, Hills R et al. Arsenic trioxide and all-trans retinoic acid treatment for acute promyelocytic leukaemia in all risk groups (AML17): results of a randomised, controlled, phase 3 trial. *The Lancet. Oncology.* 2015;16(13):1295-1305. Available at: http://www.sciencedirect.com/science/article/pii/S147020451500193X. Accessed August 2016.
12. Ma Y, Liu L, Jin J et al. All-trans retinoic acid plus arsenic trioxide versus all-trans retinoic acid plus chemotherapy for newly diagnosed acute promyelocytic leukemia: a meta-analysis. *PloS One.* 2016;11(7). Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4938459/pdf/pone.0158760.pdf. Accessed August 2016.
13. Sanz M, and Montesinos P. How we prevent and treat differentiation syndrome in patients with acute promyelocytic leukemia. *Blood.* 2014;123:2777-2782. Available at: http://www.bloodjournal.org/content/123/18/2777?sso-checked=true. Accessed August 2016.
14. Tallman M, Lo-Coco F, Barnes G et al. Cost-effectiveness analysis of treating acute promelocytic leukemia patients with arsenic trioxide and retinoic acid in the United States. *Clinical Lymphoma, Myeloma & Leukemia.* 2015;15(12):771-777. Available at:

http://www.sciencedirect.com/science/article/pii/S2152265015010666. Accessed August 2016.
15. Powell B, Moser B, Stock W et al. Arsenic trioxide improves event-free and overall survival for adults with acute promyelocytic leukemia: North American Leukemia Intergroup Study C9710. *Blood.* 2010;116(19):3751-3757. Available at: http://www.bloodjournal.org/content/116/19/3751.long?sso-checked=true. Accessed August 2016.