Realgar-indigo naturalis formulation

Essential medicine status ✓

EMLc | ATC codes: Pending

Indication	Acute myeloid leukaemia with recurrent genetic abnormalities ICD11 code: 2A60.0
Medicine type	Chemical agent
List type	Complementary
Formulations	**Oral > Solid:** 270 mg (containing tetra-arsenic tetra-sulfide 30 mg)
EML status history	First added in 2019 (TRS 1021)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Realgar-indigo naturalis formulation

Expert Committee recommendation

The Committee endorsed the recommendations of the Cancer Medicine Working Group with regard to the proposed threshold of four to six months of overall survival benefit as a guiding principle for prioritizing cancer medicines for inclusion on the EML, and applied this principle to the consideration arsenic-containing regimens for APML. The Expert Committee recommended the addition of arsenic therapies (intravenous arsenic trioxide and oral realgar-Indigo naturalis formulation) to the complementary list of the EML and EMLc for use in combination with ATRA for treatment of patients with APML, both newly diagnosed and relapsed. In consideration of a separate application of cancer medicines for children, the Committee also recommended the addition of ATRA to the EMLc, and extending the listings on the EMLc of cytarabine, daunorubicin, mercaptopurine and methotrexate to include APML. The Committee noted that treatment with ATRA plus arsenic was associated with high response rates and significant improvements in event-free and overall survival compared to ATRA plus chemotherapy, and has a more favourable toxicity profile.

Background

The application proposed the inclusion of arsenic therapies on the EML for the treatment of acute promyelocytic leukaemia (APML). Arsenic trioxide was previously considered by the Expert Committee in 2015 for treatment of APL as part of a comprehensive review of cancer medicines (1). The Committee noted that addition of arsenic trioxide as consolidation therapy for acute promyelocytic leukaemia (APML) did not produce a clinically relevant increase in overall survival in naive patients. The Committee also noted the extremely high price and low availability of arsenic trioxide and considered that this would be unaffordable in many low- and middle-income countries (LMICs). This new application focuses on clinical trial results that have been published in the past few years and examines the oral arsenic preparation realgar-Indigo naturalis formula (RIF), which has not been previously submitted. RIF represents a feasible and inexpensive alternative to intravenous arsenic trioxide that could benefit patients in LMICs. Currently listed medicines for treatment of APML on the EML are alltrans retinoic acid (ATRA), cytarabine, daunorubicin, mercaptopurine and methotrexate. These medicines are not currently included on the EMLc for this indication.

Public health relevance

The GLOBOCAN initiative estimates the worldwide incidence of new leukaemia cases for 2018 to be 437 033, with an age-

standardized rate (ASR) of 5.2 per 100 000 per year (2). Mortality was 309 006 worldwide, with an ASR of 3.5 per 100 000 per year. The ASR was higher (3.6 per 100 000) in countries with “high human development” than in countries of “low human development” (2.7 per 100 000). However, over time, differences are becoming less evident. Unfortunately, the International Agency for Research on Cancer (IARC) does not sub-classify leukaemias into acute and chronic, and myeloid or lymphoid, in its GLOBOCAN analysis. APML accounts for 10% of AML cases and its incidence in Europe is estimated to be 1/1 000 000 people (3).

Benefits

A 2009 systematic review of the effectiveness of arsenic in APML patients included five RCTs with 328 cases (4). All the RCTs focused on the comparison of ATRA plus arsenic regimen with ATRA monotherapy. Meta-analysis showed that the effect sizes for time to complete remission, two-year disease-free survival rate and relapse rate were −1.20 (95%CI −1.68 to −0.72), 8.64 (95%CI 1.66 to 45.00), and 0.21 (95%CI 0.09 to 0.47), respectively. The authors concluded that arsenic added to ATRA-based regimens improved remission rates and event-free survival. A 2019 review conducted for the UK National Institute for Health and Care Excellence (NICE) led the NICE Appraisal Committee to recommend approval of arsenic trioxide for newly diagnosed and relapsed APL (5). The review presented three RCTs, in newly diagnosed APML patients and in patients with relapsed APML. In newly diagnosed cases, results showed that more patients having ATRA plus arsenic regimen were alive at 50 months compared with people having ATRA in combination with idarubicin (99% vs 93%; p=0.007). The number of cumulative relapses at 50 months were also lower in the arsenic regimen when compared to the alternative regimen (2% vs 14%; p=0.001). At four years, results from a second trial showed a significant difference in event-free survival (91% vs 70%; p=0.002) favouring ATRA plus arsenic regimen. However, results for overall survival were less certain (93% vs 89%; p=0.250). The only included trial presented for relapsed/refractory patients compared ATRA plus arsenic regimen with arsenic regimen, a comparison that is not relevant to assess the potential benefits associated with arsenic regimens. In patients with newly diagnosed APML, several studies included and not included in the previously cited systematic reviews have confirmed the superiority of the ATRA plus arsenic regimen over ATRA/chemotherapy in children, adults and elderly patients (6–11). Many international cooperative group and single centre studies have documented the superiority of ATRA plus arsenic therapy over ATRA plus chemotherapy (usually anthracyclines), with higher remission rates, and absolute improvements in disease-free and overall survival ranging from 5% to 20% (11–21). Low-risk patients can be cured up to 98% of the time with protocols comprising ATRA plus arsenic (21, 22). The relevant advantage in the two-year event-free survival with the ATRA plus arsenic regimen is likely to be driven by the lower mortality from causes other than relapse (e.g. reduced severe haematologic toxicity as compared to chemotherapy) together with similar antileukaemic efficacy of arsenic trioxide. High-risk patients have cure rates above 85% using protocols that include ATRA, arsenic, and chemotherapy (21, 23). A 2016 meta-analysis showed that in patients treated with an ATRA plus arsenic regimen the risk of death was more than halved as compared to patients receiving ATRA plus chemotherapy (HR 0.44, 95%CI 0.24 to 0.82) (24). Arsenic-based regimens are also effective for relapsed patients with APML, many of whom (about 80%) can have their lives significantly prolonged (25–28). Although protocols with arsenic alone have proven curative for some patients on both first-line and relapsed settings, the highest cure rates have been documented with combinations of ATRA and arsenic therapy used in newly diagnosed patients. Arsenic-containing medications are now available from several suppliers in both intravenous and oral formulations, which has decreased cost and increased feasibility of arsenic-containing therapy for APML (29). Realgar-indigo naturalis formula (RIF) has proven effective in adults and children with first-line and relapsed APL in large randomized controlled trials, with event-free survival of 95%–100% for newly diagnosed patients, comparable to outcomes in the control arms that received intravenous arsenic trioxide, and five-year overall survival rates close to 90% (7, 30–34).

Harms

Arsenic-based regimens for APML are less toxic than chemotherapy-based regimens. Grade 3 or 4 neutropenia and thrombocytopenia, including episodes lasting more than 15 days, were significantly more frequent both during induction therapy and after each consolidation course in the ATRA and chemotherapy group than in the ATRA and arsenic trioxide group (11, 22, 35). However, it is associated with QTc prolongation, which can lead to cardiac dysrhythmias in patients who receive other drugs that prolong the QTc interval (36). Cardiac toxicity is rare in APML patients who receive arsenic therapy and can largely be prevented by avoiding drug–drug interactions and careful monitoring. Arsenicbased regimens have lower rates of second cancers than anthracycline-based regimens (though not statistically significant in the small studies conducted to date) (37). Finally, oral arsenic (RIF) has similar safety profile when compared to arsenic trioxide in patients with APML (38).

Cost / cost effectiveness

Arsenic trioxide was found to be highly cost-effective for relapsed APML in Canada using prices that were current prior to the

availability of generic formulations (39). Cost-effectiveness in the first-line setting would be expected to be even higher, with very high remission rates and long-term survival, and decreased need for hospitalization, blood products and supportive care. Use of an oral arsenic available at a low price point would improve cost-effectiveness even more by removing the need for daily infusions with cardiac monitoring. Costs associated with oral arsenic are about half of those associated with intravenous arsenic. In an RCT the median total medical costs were US$ 13 183.49 in the RIF group compared with US$ 24 136.98 in the arsenic trioxide group (40). The large difference in costs was mostly caused by the varying costs of maintenance treatment. During induction therapy the length of hospitalization for the RIF group was significantly shorter than that for the arsenic trioxide group (24 vs 31 days). During maintenance treatment, in the RIF group the estimated medical costs to treat a patient at home were US$ 2047.14 compared with US$ 11 273.81 to treat a patient in the arsenic trioxide group in an outpatient setting.

WHO guidelines

None available.

Availability

The United States Food and Drug Administration (FDA) approved arsenic trioxide in 2002 for relapsed APML and in 2017 for newly diagnosed patients. The European Medicines Agency (EMA) has granted marketing authorization for arsenic trioxide for newly diagnosed in relapsed APL in 2002 (provisional approval) and 2010 (full approval). Main patents have expired (2019) but secondary patents might remain active in some jurisdictions. Several generics are available (in India). Realgar-Indigo naturalis formula (RIF) is available as 270 mg tablets and it is produced by the Yifan Pharmaceutical Co (Tianchang, China). RIF contains Realgar (tetra-arsenic tetrasulfide As4S4, 30 mg per tablet), Indigo naturalis (125 mg per tablet), Radix salvia miltiorrhizae (50 mg per tablet), Radix pseudostellariae (45 mg per tablet), and garment film (a cover to contain the drug components; 20 mg per tablet) (29, 38). The dose for first-line and relapsed acute promyelocytic leukaemia is 60 mg/kg/day divided into three daily doses (20 mg/kg/dose). It is the only oral arsenic formulation commercially available and, as such, warrants special consideration, especially for use in LMICs, where the high cost of intravenous arsenic trioxide and the need for daily intravenous arsenic trioxide infusions over many months may pose important access and safety concerns.

Other considerations

Arsenic trioxide-based regimens require daily intravenous infusions during the arsenic-containing component of therapy. This means that patients must stay near the treatment centre to receive daily infusions for six weeks during remission-induction therapy followed by four four-week blocks. Infusions are given over 1–2 hours and ideally administration should occur in an infusion centre or hospital setting with availability of cardiac monitoring and resuscitation capabilities. Oral arsenic makes delivery of therapy more feasible in countries, and is of particular relevance in LMICs, where logistical and financial barriers are numerous. Diagnosis of acute promyelocytic leukaemia depends on clinical findings (haemorrhage and coagulopathy), laboratory findings (leucocytosis, anaemia, thrombocytopenia), morphology (presence of myeloid blasts containing Auer rods), and documentation of the t(15;17) chromosome translocation in the leukaemia blasts by cytogenetics, fluorescence in situ hybridization (FISH), or polymerase chain reaction (PCR). Risk stratification of patients allows each to receive the appropriate intensity of therapy to achieve cure, and includes a low-risk group, defined as patients whose presenting white blood cell count is less than 10 000 and a high-risk group (all other patients). Comments on the application were received from the WHO Department of Management of NCDs, Disability, Violence and Injury Prevention. The technical unit advised that it supported the inclusion of arsenic therapies for acute promyelocytic leukaemia on the EML. The technical unit stated that arsenic, used in combination with ATRA and chemotherapy, is curative in its use and is generally accepted as the standard of care.

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