EARLY RELEASE

New drugs

Inotuzumab ozogamicin

First published 17 June 2019
https://doi.org/10.18773/austprescr.2019.046

Approved indication: acute lymphoblastic leukaemia

Besponsa (Pfizer)
vials containing 1 mg powder for reconstitution
Australian Medicines Handbook section 14.2, Non-cytotoxic antineoplastics

Chemotherapy induces a complete remission in 60–90% of people with newly diagnosed acute lymphoblastic leukaemia. However, most of these patients will relapse. For those who relapse after chemotherapy or do not respond, the aim of subsequent treatment is complete or almost complete remission. This then allows them to have a stem cell transplant which is potentially curative.

Treatment options for these patients include:

- chemotherapy
- a tyrosine kinase inhibitor (e.g. imatinib, dasatinib or ponatinib) for those with Philadelphia chromosome (Ph)-positive disease
- blinatumomab (an anti-CD3/CD19 antibody) for those with Ph-negative disease.

Inotuzumab ozogamicin is the second immunotherapy after blinatumomab to be approved for adults with refractory or relapsed acute lymphoblastic leukaemia. This drug is a humanised monoclonal antibody specific for CD22 glycoprotein (present on most B-cell blasts) which is conjugated to a cytotoxic drug called calicheamicin. It works by binding to CD22 on cells where it is internalised. Once inside, calicheamicin is released and causes breaks in double-stranded DNA which leads to apoptosis.

Inotuzumab ozogamicin has been compared to standard chemotherapy in an open-label, phase III trial (INO-VATE) of patients with CD22-positive, Ph-positive or -negative, relapsed or refractory disease. To be eligible, they had to have at least 5% bone marrow blasts and have previously received 1–2 chemotherapy regimens.[1] In total, 326 participants were randomised 1:1 to the study drug or a standard chemotherapy regimen. Inotuzumab ozogamicin (1.8 mg/m^2/cycle) was given intravenously in three divided doses on days 1, 8 and 15 of a cycle. The first cycle lasted 21 days and subsequent cycles were 28 days. The INO-VATE study continued for two years after the last patient was randomised. Patients were treated for up to six cycles.[2]

Patients received a median of three treatment cycles of inotuzumab ozogamicin and one cycle of standard chemotherapy. In a remission analysis of 218 patients, complete or almost complete remissions (i.e. without haematologic recovery) were significantly more likely with the study drug than with standard chemotherapy (80.7% vs 29.4% of patients), except in patients carrying the Ph-positive or t(4;11) genetic abnormalities.[1] In an intention-to-treat analysis of all 326 patients, progression-free survival was significantly longer with inotuzumab ozogamicin than with chemotherapy (5 vs 1.8 months), however overall survival was only one month longer (7.7 vs 6.7 months) (see Table).[1] Two years after the start of treatment, overall survival rates with inotuzumab ozogamicin were 22.8% compared with 10% with standard chemotherapy.[2]

In a two-year safety cohort of 164 patients who took the study drug, the most common serious treatment-emergent adverse events were veno-occlusive liver disease (14%), febrile neutropenia (11.6%), pneumonia (6.1%), disease progression (4.9%), fever (3%), sepsis (2.4%), neutropenic sepsis (1.8%), septic shock (1.8%) and respiratory failure (1.2%).[2]

Table **Efficacy of inotuzumab ozogamicin in adults with refractory or relapsed acute lymphoblastic leukaemia**

Treatment	Complete or almost complete remission*	Median progression-free survival	Median overall survival
Inotuzumab ozogamicin	80.7%	5 months	7.7 months
Standard chemotherapy	29.4%	1.8 months	6.7 months

* Almost complete remission was complete remission with incomplete haematologic recovery defined as less than 1000 neutrophils/microlitre, less than 100,000 platelets/microlitre, or both.
Source: Reference 1

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

EARLY RELEASE

More patients went on to have a stem cell transplant after antibody conjugate treatment than after standard chemotherapy (48% vs 22%).[2] However, the post-transplant non-relapse mortality rate was higher with the study drug than with chemotherapy (39%, 31/79 vs 23%, 8/35). This was partly due to five fatal cases of veno-occlusive liver disease in the inotuzumab ozogamicin group.[2]

Because of the serious hepatotoxicity with this drug, it is contraindicated in anyone who has had previous veno-occlusive liver disease or ongoing liver disease such as cirrhosis or hepatitis. Liver enzymes should be checked before and after every dose as dose adjustment or discontinuation may be indicated. Liver enzymes should also be closely monitored for the first month after stem cell transplantation. Prescribers should be aware that older age and previous stem cell transplantation may increase the risk of hepatotoxicity.

There have been no clinical drug interaction studies with inotuzumab ozogamicin. QT prolongation has been reported so, if concurrent use of other drugs with the same effect cannot be avoided, an electrocardiogram and assessment of electrolytes are advisable before starting treatment.

This drug should be given intravenously over one hour. Infusion-related reactions are common after the first treatment cycle so a corticosteroid, antipyretic and antihistamine are recommended before each dose is given.

Inotuzumab ozogamicin was significantly better at inducing complete or almost complete remission than standard chemotherapy in people with relapsed acute lymphoblastic leukaemia, except for those carrying the Philadelphia chromosome or the t(4;11) mutation. In people who went on to have a stem cell transplant, a quarter developed hepatic veno-occlusive disease which was fatal in five of 18 cases.

Patients can expect to survive a median of 7.7 months with inotuzumab ozogamicin, which is only one month longer than with chemotherapy. It is unclear if inotuzumab ozogamicin will be better than blinatumomab for people with Ph-negative disease as there have been no head-to-head trials. However, when blinatumomab was compared to chemotherapy in similar patients, they also survived for 7.7 months.[3]

T manufacturer provided the product information

REFERENCES

1. Kantarjian HM, DeAngelo DJ, Stelljes M, Martinelli G, Liedtke M, Stock W, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. N Engl J Med 2016;375:740-53. https://doi.org/10.1056/NEJMoa1509277
2. Kantarjian HM, DeAngelo DJ, Stelljes M, Liedtke M, Stock W, Gökbuget N, et al. Inotuzumab ozogamicin versus standard of care in relapsed or refractory acute lymphoblastic leukemia: final report and long-term survival follow-up from the randomised, phase 3 INO-VATE study. Cancer 2019 Mar 28 [Epub ahead of print]. https://doi.org/10.1002/cncr.32116
3. Kantarjian H, Stein A, Gökbuget N, Fielding AK, Schuh AC, Ribera J-M, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med 2017; 376:836-47. https://doi.org/10.1056/NEJMoa1609783

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA and the European Medicines Agency.