New drugs

Bendamustine

Approved indication: chronic lymphocytic leukaemia, non-Hodgkin lymphoma

Ribomustin (Janssen-Cilag)

vials containing 25 mg and 100 mg powder for injection

Australian Medicines Handbook section 14.1.1

Bendamustine hydrochloride is a cytotoxic anticancer drug. It is an alkylating agent similar to chlorambucil and cyclophosphamide and is thought to interfere with cell replication by cross-linking single- and double-stranded DNA.

Bendamustine has been approved for a number of different indications in Australia:

- chronic lymphocytic leukaemia (first-line)
- in combination with rituximab for previously untreated CD20-positive indolent non-Hodgkin lymphoma and mantle cell lymphoma (in patients ineligible for autologous stem cell transplant)
- relapsed or refractory indolent non-Hodgkin lymphoma.

Chronic lymphocytic leukaemia

An open-label study randomised people, up to 75 years of age, with previously untreated chronic lymphocytic leukaemia to bendamustine or chlorambucil. To be included in the trial, patients needed to have Binet stage B (≥3 affected lymph nodes and hepatomegaly and splenomegaly) or Binet stage C (anaemia, thrombocytopenia or both regardless of the number of lymph nodes affected). After a median of six treatment cycles, progression-free survival was longer with bendamustine than with chlorambucil (see Table).[1] There were more complete responses to bendamustine than to chlorambucil (31% vs 2%). Median overall survival was not reached in the bendamustine group. However, overall survival rates were not significantly different after 84 months (see Table).[2]

Severe haematological toxicities (such as neutropenia, thrombocytopenia and anaemia) were significantly more common with bendamustine than with chlorambucil (40% vs 19%). Serious infections were also more frequent (8% vs 3%).[1]

Table **Efficacy of bendamustine in pivotal trials**

Previously untreated chronic lymphocytic leukaemia [1,2]		
	Bendamustine 100 mg/m² IV on days 1 and 2 of a 4-week cycle	**Chlorambucil orally 0.8 mg/kg on days 1 and 15 of a 4-week cycle**
Overall response[1]	68% (110/162)	31% (48/157)
Median progression-free survival[1]	21.6 months	8.3 months
Overall survival at 84 months[2]	51.3%	42.6%
Previously untreated advanced indolent non-Hodgkin or mantle cell lymphoma [3]		
	Bendamustine plus rituximab every 4 weeks‡	**Cyclophosphamide-containing regimen plus rituximab every 3 weeks§**
Overall response	93% (242/261) (104 complete responses)	91% (231/253) (76 complete responses)
Median progression-free survival	69.5 months	31.2 months
Relapsed or refractory non-Hodgkin lymphoma [4]		
	Bendamustine 120 mg/m² IV on days 1 and 2 of a 3-week cycle (up to 8 cycles)	
Overall response	75% (75/100) (17 complete responses)	
Median progression-free survival	9.3 months	

‡ bendamustine 90 mg/m² IV on days 1 and 2 and rituximab 375 mg/m² on day 1 of a 4-week cycle for up to 6 cycles

§ cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m² and rituximab 375 mg/m² on day 1 of a 3-week cycle for up to 6 cycles. Prednisolone 100 mg/day given for 5 days of each cycle.

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.

Indolent and mantle cell lymphoma

Bendamustine has also been investigated in patients with advanced indolent lymphoma and elderly patients with mantle cell lymphoma. A non-inferiority, open-label trial randomised participants to bendamustine plus rituximab or a cyclophosphamide/doxorubicin/vincristine/prednisolone combination plus rituximab. After a maximum of six treatment cycles, median progression-free survival was significantly longer with bendamustine than with the comparator (see Table).[3] Overall responses were similar but complete responses were more common with bendamustine. Median overall survival was not reached but the number of deaths was similar in both treatments (43/261 with bendamustine, 45/253 with comparator).[3]

Haematological toxicities were less common with bendamustine and rituximab than with the cyclophosphamide regimen (30% vs 68%), as were infections (37% vs 50%), peripheral neuropathy (7% vs 29%) and stomatitis (6% vs 19%). Conversely erythmatous skin reactions were more frequent in people receiving bendamustine.[3] Bendamustine did not cause hair loss.

Relapsed or refractory indolent lymphoma

Currently there is no standard treatment for patients with relapsed or refractory indolent lymphoma. A single-arm trial enrolled patients who were not responding to rituximab or whose disease had progressed. After a median of six treatment cycles, three-quarters of the patients had responded to bendamustine (see Table).[4] However, response rates were better in patients who had been sensitive to their last treatment compared to those with refractory disease (88% vs 64%), as was progression-free survival (11.8 vs 7.5 months).[4]

In the trial, anaemia, thrombocytopenia and neutropenia were the most common adverse events with bendamustine and occurred in most patients. Of the non-haematological events, nausea (77%), infection (69%), fatigue (64%), diarrhoea (42%), vomiting (40%), fever (36%), constipation (31%), anorexia (24%), headache (21%) and stomatitis (21%) were the most common. The most frequently occurring infections included urinary tract infections, pneumonia and sinusitis. There were five cases of cytomegalovirus infection. Two patients had a secondary malignancy – myelodysplastic syndrome and squamous cell carcinoma. Seven patients died as a result of a serious adverse event – causes included cytomegalovirus pneumonia, pneumonia with diffuse intra-alveolar haemorrhage and thrombocytopenia, pneumonia with sepsis, respiratory failure, chronic obstructive pulmonary disease with neutropenia, and cardiopulmonary arrest.[4]

Precautions

As myelosuppression is so common with bendamustine, blood counts should be monitored at least weekly. Treatment is contraindicated with low blood counts (leukocyte $<3 \times 10^9$/L or platelets $<75 \times 10^9$/L). Patients should be warned about the risk of infections, including respiratory problems, and advised to seek medical attention if symptoms develop. Infections, particularly those involving leukocytopenia, are a contraindication to treatment.

Skin reactions with bendamustine are common and treatment should be stopped if reactions progress. Serum potassium should be closely monitored in patients with cardiac disorders. Supplementation and an ECG are needed if serum potassium falls below 3.5 mmol/L.

Tumour lysis syndrome has been reported with bendamustine, usually within two days of treatment, so monitoring is important. Adequate hydration and close monitoring of serum potassium and uric acid are recommended as prophylactic measures. Allopurinol can be prescribed during the first two weeks but has occasionally been associated with Stevens-Johnson syndrome and toxic necrolysis.

Infusion reactions such as fever, chills and rash can occur with bendamustine, and antihistamines, antipyretics and corticosteroids are recommended. Anaphylaxis, although rare, has been reported and hypersensitivity to bendamustine is a contraindication to treatment. Other contraindications include major surgery in the previous month, yellow fever vaccination and breastfeeding.

Bendamustine is a category D pregnancy drug. There are no data in women but the drug was toxic and teratogenic in animals. Contraception is recommended in women and men being treated. Like other alkylating agents, irreversible infertility may occur in men.

After an intravenous infusion over 30–60 minutes, bendamustine is rapidly cleared by hydrolysis, and conjugation with glutathione. The elimination half-life is around 30 minutes with half the dose recovered in urine and a quarter in faeces. Bendamustine is contraindicated in people with severe hepatic impairment (serum bilirubin 51.3 micromol/L) or those with jaundice.

Hepatic metabolism of bendamustine involves cytochrome P450 (CYP) 1A2 so there is a potential for drug interactions with CYP1A2 inhibitors such as fluvoxamine, ciprofloxacin, acyclovir and cimetidine. Based on in vitro data, inhibitors of transporters such as P-glycoprotein may increase exposure to bendamustine.

Conclusion

Bendamustine as monotherapy, or in combination with rituximab, seems to improve disease control in people with slow-growing B cell malignancies. However, it has not so far been found to improve overall survival. Bendamustine causes more adverse effects than chlorambucil but fewer than a cyclophosphamide/doxorubicin/vincristine/prednisolone regimen. Myelosuppression and infections are common and are likely to limit treatment in some patients.

T manufacturer provided the product information

REFERENCES *†

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The Transparency score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2014;37:27.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov)

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu)