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

Bendamustine in combination with rituximab (MabThera®) for the treatment of previously untreated and relapsed mantle cell lymphoma

April 2017
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ONE WALES INTERIM COMMISSIONING DECISION

Bendamustine in combination with rituximab (MabThera®) for the treatment of previously untreated and relapsed mantle cell lymphoma

Date of advice: April 2017

The following Interim Pathways Commissioning Group (IPCG) recommendation has been endorsed by health board Chief Executives.

Bendamustine in combination with rituximab can be made available within NHS Wales for the treatment of previously untreated and relapsed mantle cell lymphoma in patients currently deemed unsuitable for anthracycline-based therapy or other health technology appraisal-approved regimens.

Bendamustine in combination with rituximab is not a licensed regimen to treat this indication and is therefore 'off-label'. Each provider organisation must ensure all internal governance arrangements are completed before these medicines are prescribed in combination.

The risks and benefits of the off-label use of bendamustine with rituximab for this indication should be clearly stated and discussed with the patient to allow informed consent.

Providers should consult the General Medical Council Guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

This advice will be reviewed after 12 months or earlier if new evidence becomes available

New safety alert
Following this recommendation, in May 2017 a letter was sent out to healthcare professionals from Astellas in agreement with the Medicines and Healthcare products Regulatory Agency (MHRA). The letter highlighted new safety information regarding a risk of increased mortality associated with use of bendamustine when used in non-approved combination treatments or outside approved indications. Fatal toxicities were mainly due to opportunistic infections. Prescribers should consult the safety information prior to prescribing. All suspected adverse drug reactions (ADRs) that are serious or result in harm should be reported to the MHRA via the Yellow Card Centre Wales.

This advice will be reviewed after 12 months or earlier if new evidence becomes available.
One Wales advice promotes consistency of access across NHS Wales.

KEY FINDINGS: This is an abbreviated summary of the evidence provided to IPCG

Report background
Bendamustine is available through NHS England's Cancer Drugs Fund for off-label use in the first-line treatment of mantle cell lymphoma, in people for whom standard treatment is unsuitable. According to the Cancer Drugs Fund criteria, bendamustine may be used in combination with rituximab, which is commissioned by NHS England for this indication. Although rituximab is not licensed for treating mantle cell lymphoma, the National Institute for Health and Care Excellence (NICE) mantle cell pathway recommends it in combination with chemotherapy as first-line treatment of advanced-stage mantle cell lymphoma.

A cohort of patients has been identified through data from individual patient funding request (IPFR) panels and clinicians in Wales consider there is an unmet need within the service. This cohort includes people with untreated and relapsed mantle cell lymphoma for whom anthracycline-based chemotherapy is unsuitable. Based on this unmet need this medicine combination was therefore considered suitable for assessment via the One Wales process.

Efficacy/Effectiveness
Data from a phase III study showed that bendamustine plus rituximab was more effective and less toxic than rituximab plus CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) in first-line treatment of mantle cell lymphoma. Data from a second phase III study showed that bendamustine plus rituximab was superior to rituximab plus CHOP/CVP (cyclophosphamide, vincristine and prednisolone).

Data from a phase III study showed that bendamustine plus rituximab was more effective than fludarabine plus rituximab in treating relapsed mantle cell lymphomas, giving a longer progression-free survival and median overall survival.

Further evidence considers bendamustine plus rituximab plus cytarabine for first-line and following first relapse. Overall response rates and progression-free survival were higher than those reported in the phase III bendamustine with rituximab studies, however, these studies did not include a comparator arm and patient numbers were small.

Safety
Bendamustine plus rituximab is associated with high incidences of serious haematological toxicities, in common with other chemotherapy regimens used to treat mantle cell lymphoma. The phase III studies showed that bendamustine plus rituximab has a safety profile that is distinct from those of the standard chemotherapy regimens, and has some favourable aspects. In the first-line treatment of mantle cell lymphoma bendamustine plus rituximab showed a generally lower incidence of neutropenia, leukopenia, alopecia and neuropathy than was seen in patients treated with rituximab plus CHOP, with a higher incidence of skin reactions and drug sensitivity. A Cochrane review of bendamustine in treating indolent B cell lymphoid malignancies concluded that the risk of grade 3–4 adverse events was similar when bendamustine was compared with CHOP and fludarabine. Clinical expert opinion suggests that haematological toxicity is higher when adding cytarabine to the bendamustine plus rituximab combination.

Patient factors
Health-related quality of life data showed that first-line treatment with bendamustine plus rituximab was associated with small improvements in functioning compared with standard therapy. No data were identified for assessing the health-related quality of life in the relapsed setting.

Cost effectiveness
No cost-effectiveness analyses were identified for bendamustine plus rituximab for the treatment of mantle cell lymphoma.

Budget impact
Based on an estimated 12 patients with mantle cell lymphoma eligible for treatment the annual budget impact is £6,864. This analysis focuses on bendamustine acquisition costs only because patients would receive rituximab as part of an alternative regimen so rituximab does not represent an additional cost. Additional resource costs for one extra day of medicine administration per cycle for bendamustine will be dependent upon current service capacity. Some patients are already receiving this regimen through

IPFR and local applications though accurate figures were not available from the health boards. In addition, alternative regimens are similarly priced and therefore the true net cost is likely to be lower than £6,684.

Welsh commercial access agreement
These medicines are currently not licensed for the indication being considered (i.e. off-label). Therefore a commercial agreement cannot be offered by the relevant companies because the Pharmaceutical Industry's code of practice prevents a company from promoting an off-label use of a medicine.

Impact on health and social care services
Using bendamustine plus rituximab to treat mantle cell lymphoma, including newly diagnosed and relapsed disease, is expected to have minimal impact on existing services.

Innovation and/or advantages
Bendamustine plus rituximab offers an anthracycline-free regimen for the treatment of mantle cell lymphoma. It therefore may be suitable for people who are unable to tolerate or who have a contra-indication to an anthracycline-based regimen, or who may have reached the maximum cumulative dose of anthracycline at which the risk of chronic cardiotoxicity increases.