polatuzumab vedotin (POLIVY°) and large B-cell lymphoma

NOT ACCEPTABLE

A single randomised comparative trial with numerous methodological flaws evaluated the addition of *polatuzumab vedotin* to a drug combination which is relevant in this situation.

POLIVY° - *polatuzumab vedotin* powder for concentrate for solution for intravenous infusion

- **140 mg** of *polatuzumab vedotin* per vial

antineoplastic; cytotoxic drug conjugated to an anti-CD79b monoclonal antibody

Indication: relapsed or refractory diffuse large B-cell lymphoma, in combination with *bendamustine* and *rituximab,* in adults who are not candidates for haemopoietic stem cell transplantation. [EU centralised procedure - orphan drug]

Diffuse large B-cell lymphoma is an aggressive form of non-Hodgkin lymphoma. The first-line treatment is R-CHOP chemotherapy, a combination of *rituximab* + *cyclophosphamide* + *doxorubicin* + *vincristine* + *prednisolone*. If the disease is refractory to or relapses after this first line of treatment, a second chemotherapy regimen is used, often containing a platinum compound and *rituximab*. A haemopoietic stem cell transplant is sometimes offered. There is no consensus over which chemotherapy regimen to use after several successive relapses. CAR T-cell therapy (a type of immunotherapy in which patients are injected with their own T cells that have been genetically modified to destroy the malignant cells) is sometimes an option in this situation (1,2). The *bendamustine* + *rituximab* combination has not been evaluated in comparative randomised trials in this situation. It has not been shown to extend survival. And, as of autumn 2020, it is not included among the options recommended in European guidelines (2-4).

Polatuzumab vedotin is an anti-CD79b monoclonal antibody conjugated to monomethyl auristatin E, a drug, like the taxanes, whose cytotoxic action is based on microtubule disruption. *Polatuzumab vedotin* (Polivy°, Roche) as an adjunct to *bendamustine* + *rituximab* has been granted conditional European marketing authorisation for use in adults with relapsed or refractory diffuse large B-cell lymphoma who are not candidates for haemopoietic stem cell transplantation (5,6).

Clinical evaluation of *polatuzumab vedotin* in this situation is mainly based on one non-blinded randomised trial in 80 patients that compared *polatuzumab vedotin* + *bendamustine* + *rituximab* versus *bendamustine* + *rituximab*. The strength of evidence provided by this trial was greatly reduced by its numerous methodological flaws: an irrelevant comparator was used; the highly heterogeneous patient characteristics and the imbalance between the groups favoured *polatuzumab vedotin* (especially with regard to the reasons for ineligibility for transplantation and factors linked to disease prognosis); and there were no statistical hypotheses in the trial protocol, reducing the reliability of the statistical tests performed. After a median follow-up of 22 months, median survival appeared longer in the *polatuzumab vedotin* group. But given the comparator that was chosen, this finding does not show whether or not *polatuzumab vedotin* is useful in this clinical situation (6,7).

The main adverse effects of microtubule-disrupting cytotoxic drugs, such as taxanes, are: neuropathy; haematological, cutaneous and gastrointestinal disorders; and arthralgia and myalgia (5). Allergic reactions are likely due to the protein portion (the monoclonal antibody) of *polatuzumab vedotin*. In the trial mentioned above, serious adverse events were reported in 64.4% of patients in the *polatuzumab vedotin* group, versus 61.5% of those in the comparator group. The adverse events reported more frequently with *polatuzumab vedotin* than with the comparator were mainly: anaemia (47% versus 26%), thrombocytopenia (47% versus 28%), neutropenia (47% versus 39%), diarrhoea (38% versus 28%), infusion reactions (33% versus 23%), peripheral neuropathy (20% versus 3%) and pneumonia (16% versus 10%) (6).

Polatuzumab vedotin is metabolised by the cytochrome P450 isoenzyme CYP3A4. It is also a P-glycoprotein substrate. Numerous pharmacokinetic interactions are to be expected (6).

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Literature search up to 7 October 2020

In response to our request for information, Roche provided us with administrative documents, published articles and packaging items.

1- Prescrire Editorial Staff "Axicabtagene ciloleucel - Yescarta°. In certain types of lymphoma when other treatment options have been exhausted: a CAR T-cell therapy that increases the chances of survival but frequently provokes serious adverse effects" *Prescrire Int* 2019; **28** (208): 229-231.

2- BMJ Best Practice "Non-Hodgkin's lymphoma" 15 March 2019: 96 pages.

3- Freedman AS et al. "Treatment of relapsed or refractory diffuse large B cell lymphoma" UpToDate. www.uptodate.com accessed 2 October 2020: 46 pages.

4- Tilly H et al. "Diffuse large B-cell lymphoma: ESMO Clinical Practice Guidelines" *Ann Oncol* 2015; **26** (suppl. 5): v116-v125.

5- Prescrire Rédaction "Brentuximab védotine (Adcetris°). Un intérêt à mieux cerner" *Rev Prescrire* 2012; **32** (349): 814-818.

6- EMA - CHMP "Public assessment report for Polivy. EMEA/H/C/004870/0000" 14 November 2019: 159 pages.

7- HAS - Commission de la Transparence "Avis-Polivy" 10 June 2020: 29 pages.