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CADTH Drug Implementation Advice

Provisional Funding Algorithm

Adult B-Cell Precursor Acute Lymphoblastic Leukemia, Philadelphia Chromosome Negative

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

1. Background

CADTH has reviewed and issued recommendations for drugs that can be used in adults with B-cell precursor acute lymphoblastic leukemia (BCP-ALL) that is Philadelphia chromosome negative (Ph-). Based on the 2018 review of inotuzumab ozogamicin (Besponsa) for the treatment of relapsed or refractory BCP-ALL, through the CADTH pan-Canadian Oncology Drug Review (pCODR), the pan-Canadian Oncology Drug Review Expert Review Committee (pERC) issued the following reimbursement recommendation:

pERC recommendation for inotuzumab ozogamicin (Besponsa)
pERC recommends the reimbursement of inotuzumab ozogamicin (Besponsa) for the treatment of relapsed or refractory BCP-ALL, only if the following condition is met: • cost-effectiveness is improved to an acceptable level.

BCP-ALL = B-cell precursor acute lymphoblastic leukemia; pERC = pan-Canadian Oncology Drug Review Expert Review Committee.

Based on the 2017 review of blinatumomab (Blincyto) for the treatment of adult patients with Ph- relapsed or refractory BCP-ALL and the 2020 review of blinatumomab (Blincyto) for the treatment of Ph-, CD19 positive (CD19+) BCP-ALL in adult and pediatric patients who are in first or second hematologic complete remission (CR) and are minimal residual disease positive (MRD+), pERC issued the following reimbursement recommendations:

pERC recommendations for blinatumomab (Blincyto)
pERC recommends the reimbursement of blinatumomab (Blincyto) for the treatment of adult patients with Ph- relapsed/refractory BCP-ALL, only if the following condition is met: • cost-effectiveness is improved to an acceptable level.
pERC recommends the reimbursement of blinatumomab (Blincyto) for the treatment of Ph–, CD19+, BCP-ALL adult and pediatric patients who are in first or second hematologic CR and are minimal residual MRD+, only if the following condition is met: • cost-effectiveness is improved to an acceptable level.

BCP-ALL = B-cell precursor acute lymphoblastic leukemia; CD19+ = cluster of differentiation 19 positive; CR = complete response; MRD+ = minimal residual disease positive; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; Ph-- = Philadelphia chromosome negative.

At the request of the participating drug programs, CADTH convened a panel of Canadian clinical experts to provide advice for addressing the outstanding implementation issues as follows.

Implementation Issues

- Use of inotuzumab ozogamicin for adult patients with relapsed ALL who have been previously treated with blinatumomab in the setting of MRD+ Ph- ALL in a first or second hematological CR.
- Re-treatment with blinatumomab in relapsed BCP-ALL patients who were previously treated with blinatumomab in the relapsed setting for fewer than 4 cycles as a bridge to transplant.

2. Consultation Process and Objectives

The implementation advice panel comprised four Canadian specialists with expertise in the diagnosis and management of patients with ALL, a representative from a public drug program, and a panel chair. The objective of the panel was to provide advice to the participating drug programs regarding the implementation issues noted in section 1. A consensus-based approach was used, and input from stakeholders was solicited using questionnaires. Stakeholders including patient and clinician groups and pharmaceutical manufacturers, and public drug programs were invited to provide input in advance of the meeting.

The advice presented in this report is not necessarily evidence-based, but has been developed based on the experience and expertise of the implementation advice panel members, and as such represents experience-informed opinion.

3. Advice on Funding Algorithm

3.1 Summary of Implementation Advice

Implementation advice regarding the optimal sequencing of treatments is summarized in Table 1. For each implementation issue, a summary of the relevant panel discussion is provided for additional context.

Table 1: Summary of Advice for Addressing Implementation Issues

Issue	Advice
Use of inotuzumab ozogamicin for adult patients with relapsed ALL who have been previously treated with blinatumomab in the setting of MRD+, Ph- ALL in first or second hematological CR.	The panel advises that inotuzumab ozogamicin should be used for adult patients with relapsed ALL who have been previously treated with blinatumomab in the setting of MRD+, Ph- ALL. The panel suggests that in this situation, inotuzumab ozogamicin should be used for curative intent therapy.
Re-treatment with blinatumomab in relapsed patients who were previously treated with blinatumomab in the relapsed setting for fewer than 4 cycles as a bridge to transplant.	The panel advises that for patients treated with fewer than 4 blinatumomab cycles in the relapsed setting, the preference would be to use inotuzumab; however, if this is not possible, blinatumomab could be used in patients with a beneficial first response to blinatumomab and who were in longer remission (≥ 6 months).

ALL = acute lymphoblastic leukemia; CR = complete remission; Ph- ALL = Philadelphia chromosome acute lymphoblastic leukemia; MRD+ = minimal residual disease positive.

In addition to the advice above, the panel indicated that given that an improvement in cost-effectiveness was a condition for reimbursement that was consistent in each of the recommendations noted above, implementation of any advice herein should be contingent upon ensuring that the relevant treatments are affordable to public payers.

3.2 Panel Discussion

3.2.1 Sequential use of inotuzumab ozogamicin after first-line blinatumomab for MRD positive Ph- ALL

The use of inotuzumab ozogamicin for adult patients with relapsed ALL who have been previously treated with blinatumomab in the setting of MRD+ Ph- ALL in first or second

hematological CR was raised as an implementation issue to the panel. The panel agreed that they would support the use of inotuzumab for adult patients with relapsed ALL who have been previously treated with blinatumomab in this setting. Panellists propose that access to inotuzumab at relapse should be reserved for cases where the therapeutic intention is curative; that is, patients who would be eligible for cellular therapy if response to inotuzumab is achieved. Cellular therapy can be defined as stem cell transplantation and chimeric antigen receptor (CAR) T-cell therapy. Patients who were never fit for cellular therapy and/or are being treated with a palliative intent would not be good candidates for subsequent inotuzumab ozogamicin. Panellists mentioned that this situation would affect a very small portion of patients; however, it would be important to have these agents as viable options for appropriate patients. Panellists agreed that there is currently limited evidence for this scenario; one small trial[1] has been conducted in this therapeutic space with six patients. While evidence in this space is limited, available data in other populations and settings have shown that ALL patients can have a significant time in remission from treatment with inotuzumab after blinatumomab. One recent retrospective study[2] (where 13 patients received inotuzumab and eight patients were re-challenged with blinatumomab), although small, does document the use of either inotuzumab or blinatumomab after blinatumomab failure and noted that both blinatumomab and inotuzumab can salvage a proportion of these patients with superior results whether or not the patients proceeded to additional cellular therapy. The median survival of patients treated with inotuzumab from time of blinatumomab failure was 14 months.[2]

Panellists stated that inotuzumab produces a higher CR rate and MRD– state than salvage chemotherapy in relapsed or refractory ALL. Regardless of the state of disease, the outcome of MRD– disease after treatment is consistently superior. The likelihood of a curative outcome with inotuzumab in patients previously treated with blinatumomab would be higher than re-treating with chemotherapy. Chemotherapy treatment has significant indirect costs and can negatively impact inpatient quality of life (QoL). Panellists agreed that inotuzumab is better for administering to patients in the relapsed and refractory setting because it is more likely to control disease in preparation for subsequent therapy in this setting and results in a better QoL for the patient. Panellists mentioned that there has been no new safety concerns when blinatumomab and inotuzumab have been followed by one or the other in recent treatment protocols, in either the upfront or relapsed setting. The panellists indicated that there is currently safety data for patients receiving inotuzumab ozogamicin after blinatumomab, but not specifically in the setting of being used for the purpose of MRD clearance. Clinicians would have to infer that the safety would be the same between both populations. If blinatumomab is used in the frontline setting, for MRD+ disease, the panellists believed that it would make sense to try a different agent targeting a different antigen at relapse even if there is no evidence of antigen escape.

The panellists noted that if the relapsed cells continued to express CD22, they did not see any reason to restrict access to inotuzumab, in order to provide the best options to produce the best outcome for these patients. The panellists stated that this type of situation will only apply to a small minority of patients as many of the patients in this category will not be appropriate for any therapy and some of these patients will have other options such as chimeric antigen receptor (CAR) T-cell therapy. However, in patients for whom it would be appropriate, inotuzumab could provide a period of prolonged remission or a bridge to cellular therapy or other therapy.

3.2.2 Post-transplant re-treatment with blinatumomab in the relapsed setting

Re-treatment with blinatumomab in relapsed patients who were previously treated with blinatumomab for fewer than four cycles as a bridge to transplant was raised to the panel as an outstanding implementation issue for jurisdictions. Panellists agreed that in this situation the preference would be to use inotuzumab ozogamicin; however, if this is not a possibility, blinatumomab could be used under certain circumstances. The panel further noted that re-treatment with blinatumomab could be beneficial for a subset of patients who have not received the total cycles of treatment. The evidence to inform the use of blinatumomab in relapsed patients who were previously treated with this drug in the relapsed setting for 1 to 2 cycles as a bridge to transplant is sparse. However, the panellists noted that outcomes of MRD- disease after treatment are consistently superior to MRD+ disease, and that blinatumomab produces higher CR and negative MRD rates than salvage chemotherapy. A recent publication indicated that among patients who relapsed after receiving blinatumomab, re-treatment with blinatumomab was most successful in those who were sensitive to blinatumomab initially, and likely had at least a six-month remission before relapse. This resulted in a median survival of 17 months after blinatumomab failure, supporting the use of blinatumomab in the post-transplant relapsed setting.[2-4]

The panellists stated that this re-treatment setting would only be beneficial for a very small subset of patients. Based on clinical experience, this was estimated to be about 50 of the total adult ALL patients across the country (which was estimated at about 300 to 500 patients) per year.

3.3 Provisional Funding Algorithm

Figure 1 depicts the provisional funding algorithm as proposed by the panel. Note that this diagram is a summary representation of the drug funding options for the condition of interest. It is not a treatment algorithm and is neither meant to detail the full clinical management of each patient nor the provision of each drug regimen. The diagram may not contain a comprehensive list of all available treatments, and some drugs may not be funded in certain provinces. All drugs are subject to explicit funding criteria, which may also vary between provinces. Readers are invited to refer to the individual drug entries on the CADTH website for more details.

3.3.1 First-line setting

Untreated fit adult patients with BCP-ALL that is Ph- are first treated with intensive multiagent induction chemotherapy. Following induction, hematologic response is assessed. Patients who do not show a CR and are deemed refractory can be offered subsequent treatments in this setting. For patients showing a CR, the MRD status is assessed. MRD+ patients can be offered blinatumomab therapy. MRD- patients after chemotherapy and those treated with blinatumomab can be further treated with maintenance chemotherapy or considered for allogeneic stem cell transplantation (allo-SCT) as long as they show good response to the frontline therapies. In MRD- patients who have not received blinatumomab, eligibility for the latter can be reassessed should there be a change in MRD status. Less fit patients may be treated with lower intensity chemotherapy upfront, but would not be eligible for blinatumomab in this setting.

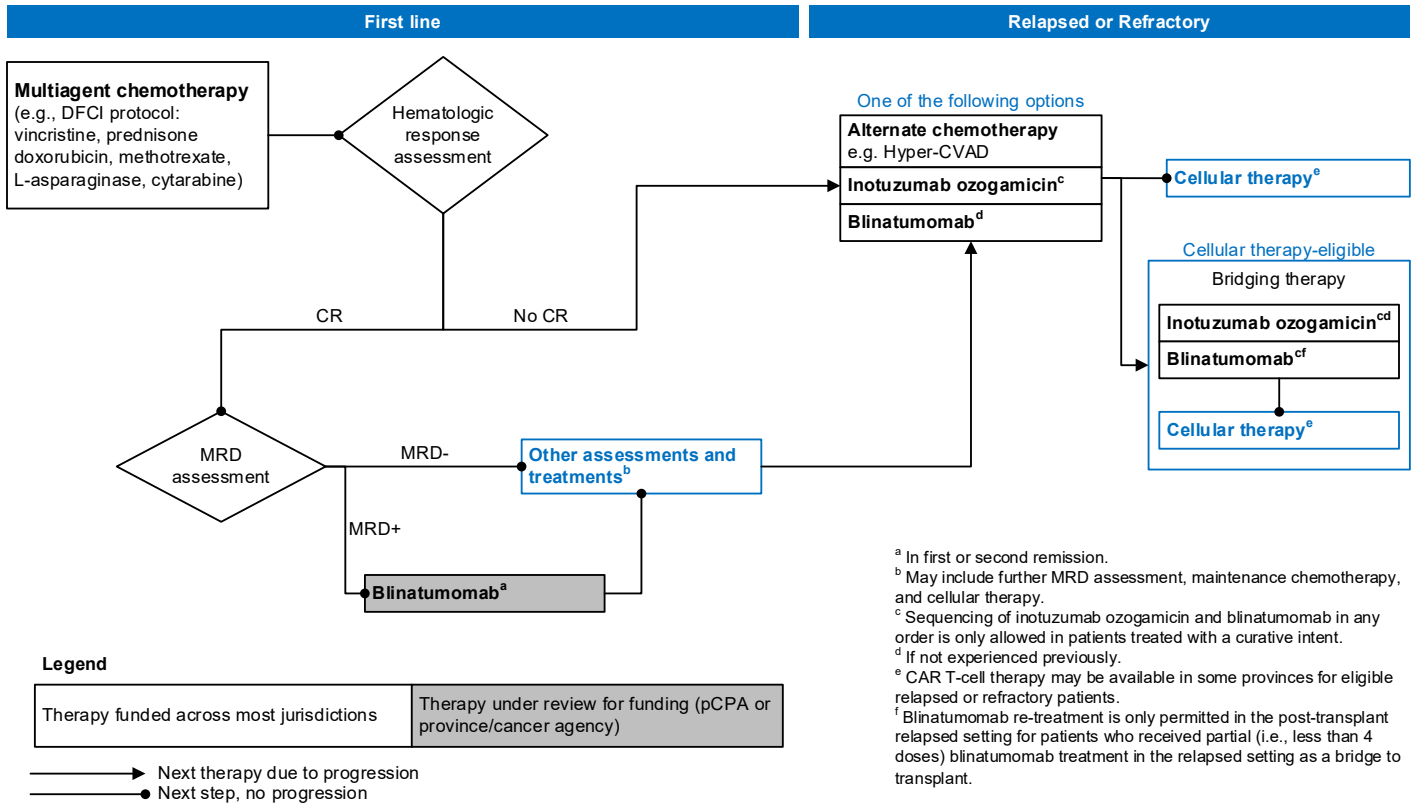
3.3.2 Relapsed or refractory

Patients refractory to induction chemotherapy or in first relapse can be treated with one of the following:

- alternative chemotherapy
- blinatumomab if not previously received in the setting of MRD+ CR
- inotuzumab; however, patients who received blinatumomab for MRD+ disease in CR are only eligible for inotuzumab if treatment intent is curative.

Patients who respond to the above treatments may be eligible for cellular therapy. Upon subsequent relapse or if refractory, patients being treated with curative intent may go on to receive blinatumomab or inotuzumab ozogamicin as a bridge to cellular therapy if they had not previously received that drug.

Figure 1: Provisional Funding Algorithm Diagram for Ph- BCP-ALL Eligible for Upfront Intensive Chemotherapy



CAR T-cell = chimeric antigen receptor T-cell; CR = complete response; hyper-CVAD = hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; DFCI = Dana Farber Cancer Institute; MRD = minimal residual disease; pCPA = pan-Canadian Pharmaceutical Alliance.

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