Health Quality Ontario

Minimal Residual Disease Evaluation in Childhood Acute Lymphoblastic Leukemia: OHTAC Recommendation

ONTARIO HEALTH TECHNOLOGY ADVISORY COMMITTEE RECOMMENDATIONS

- The Ontario Health Technology Advisory Committee recommends publicly funding minimal residual disease evaluation for pediatric management of acute lymphoblastic leukemia

RATIONALE FOR THE RECOMMENDATION

Leukemia accounts for nearly a third of childhood cancers in Canada, with acute lymphoblastic leukemia comprising nearly 80% of cases. Despite treatment advances in recent decades, nearly a quarter of patients who are considered to be at standard risk still suffer a relapse. Relapse is thought to result from extremely low levels of leukemic cells left over once complete remission is reached, termed minimal residual disease (MRD).

Health Quality Ontario conducted an evidence review to further elucidate the relationship between MRD and event-free survival by looking at relapse, the primary determinant of event-free survival and the biological mechanism through which MRD is thought to act, and to assess the effect of MRD-directed treatment on patient-important outcomes in childhood acute lymphoblastic leukemia.[1] Health Quality Ontario also commissioned the Toronto Health Economics and Technology Assessment Collaborative to provide economic evidence on the topic.[2] The clinical and economic assessments are available separately.[1,2] A completed "decision determinants" framework is included as an appendix to this report.

A positive MRD result in patients with acute lymphoblastic leukemia is a significant, independent prognostic factor for relapse when measured in de novo acute lymphoblastic leukemia, evaluated at the end of induction; de novo acute lymphoblastic leukemia, evaluated at the end of consolidation; relapsed acute lymphoblastic leukemia, evaluated after re-induction; and recipients of hematopoietic stem cell transplant, evaluated before transplantation.

In clinically standard- and intermediate-risk patients with acute lymphoblastic leukemia, MRD-directed treatment selection was beneficial in that:

- MRD–low-risk patients receiving MRD-directed treatment reduction experienced no compromise of event-free survival, overall survival, or relapse risk reduction compared with standard treatment

ABOUT OHTAS

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- MRD–high-risk patients receiving MRD-directed treatment augmentation experienced a significant benefit in event-free survival and relapse risk reduction compared with standard treatment. The trial did not show a benefit in overall survival

MRD testing by flow cytometry versus no testing improves clinical outcomes in newly diagnosed patients with precursor B-cell acute lymphoblastic leukemia over their lifetime, and it represents good value for money, with an incremental cost-effectiveness ratio (ICER) of $43,613 per quality-adjusted life-year gained in the base-case analysis.

The budget impact analysis forecasts that the economic burden of MRD testing in patients with precursor B-cell acute lymphoblastic leukemia over 3 years is approximately $1.3 million and over 5 years is approximately $2.4 million.

The Ontario Health Technology Advisory Committee accepted the findings of the clinical and economic assessments, and decided to recommend in favour of public funding.

Decision Determinants for Minimal Residual Disease Evaluation in Childhood Acute Lymphoblastic Leukemia

Decision Criteria	Subcriteria	Decision Determinants Considerations
Overall clinical benefit How likely is the health technology/intervention to result in high, moderate, or low overall benefit?	**Effectiveness** How effective is the health technology/intervention likely to be (taking into account any variability)? **Safety** How safe is the health technology/intervention likely to be?	Childhood ALL is the most common pediatric cancer. There are approximately 100 new cases of ALL per year in Ontario. Good survival can be achieved overall with contemporary treatment; however, ~25% of patients considered standard risk on the basis of clinical factors still relapse, which is the primary determinant of morbidity and mortality. MRD evaluation requires a bone marrow sample, which is a routine procedure throughout ALL treatment.
	Burden of illness What is the likely size of the burden of illness pertaining to this health technology/intervention? **Need** How large is the need for this health technology/intervention?	Despite heterogeneity in research methods (sample size, MRD cut-points, statistical analysis and confounders adjusted for), a positive MRD result in patients with ALL was a significant, independent prognostic factor for relapse when measured in each of the following scenarios: • In de novo ALL, evaluated at the end of induction (GRADE: Low) • In de novo ALL, evaluated at the end of consolidation (GRADE: Moderate) • In relapsed ALL, evaluated after re-induction (GRADE: Moderate) • In HSCT recipients, evaluated before transplantation (GRADE: Moderate) In clinically standard- and intermediate-risk patients with ALL, MRD-directed treatment selection was beneficial in that: • MRD–low-risk patients receiving MRD-directed treatment reduction experienced no compromise of EFS, OS, or relapse risk reduction compared with standard treatment (GRADE: Moderate) • MRD–high-risk patients receiving MRD-directed treatment augmentation experienced a significant benefit in EFS and relapse risk reduction compared with standard treatment (GRADE: Moderate). The trial did not show a benefit in OS (GRADE: Low)
Consistency with expected societal and ethical values[a] How likely is adoption of the health technology/intervention to be congruent with societal and ethical values?	**Societal values** How likely is the adoption of the health technology/intervention to be congruent with expected societal values?	Childhood ALL represents a substantial portion (~80%) of pediatric leukemia and is associated with substantial morbidity and mortality. Improving the diagnosis and treatment of children with ALL can increase the longevity and quality of life of survivors and their families. Adoption of MRD evaluation is likely to be congruent with expected societal and ethical values.
	Ethical values How likely is the adoption of the health technology/intervention to be congruent with expected ethical values?	According to local experts, MRD evaluation is now standard of care. Clinicians think that it is unethical to treat patients without considering MRD. Further studies to establish the effectiveness of MRD evaluation and MRD-directed treatments are likely to be limited given the well-established poor prognosis of MRD-positive patients.

Decision Criteria	Subcriteria	Decision Determinants Considerations
Value for money How efficient is the health technology likely to be?	**Economic evaluation** How efficient is the health technology/intervention likely to be?	Our economic modeling study, relevant to the Ontario setting, shows that compared with no testing, MRD testing by flow cytometry in newly diagnosed patients with precursor B-cell ALL represents good value for money at commonly used willingness-to-pay thresholds of $50,000/QALY and $100,000/QALY.
Feasibility of adoption into health system How feasible is it to adopt the health technology/intervention into the Ontario health care system?	**Economic feasibility** How economically feasible is the health technology/intervention?	The 1-year cost expenditure for MRD testing by flow cytometry at the end of induction and consolidation in patients with precursor B-cell ALL is $340,760. This budget impact estimate includes the costs of testing and downstream costs of treatment.
	Organizational feasibility How organizationally feasible is it to implement the health technology/intervention?	The POGO MRD Working Group has posited (following initial cost investigation) that it could be less expensive to test for MRD in Ontario than to send samples out of country on a fee-for-service model to US reference laboratories. The MRD Working Group is developing a plan for implementation of MRD evaluation in Ontario, making use of the existing Toronto site ready in June 2016 as a local reference laboratory, including development of standardized flow cytometry protocols.

Abbreviations: ALL, acute lymphoblastic leukemia; EFS, event-free survival; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HSCT, hematopoietic stem cell transplant; MRD, minimal residual disease; OS, overall survival; POGO, Pediatric Oncology Group of Ontario; QALY, quality-adjusted life-year.

[a]Anticipated or assumed common ethical and societal values held in regard to the target condition, target population, or treatment options. Unless there is evidence from scientific sources to corroborate the true nature of the ethical and societal values, the expected values are considered.

REFERENCES

(1) Health Quality Ontario. Minimal residual disease evaluation in childhood acute lymphoblastic leukemia: a clinical evidence review. Ont Health Technol Assess Ser [Internet]. 2016 March;16(7):1-52. Available from: http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations/ontario-health-technology-assessment-series/eba-mrd

(2) Health Quality Ontario and the Toronto Health Economics and Technology Assessment Collaborative. Minimal residual disease evaluation in childhood acute lymphoblastic leukemia: an economic analysis. Ont Health Technol Assess Ser [Internet]. 2016 March;16(8):1-83. Available from: http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations/ontario-health-technology-assessment-series/econ-mrd

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