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Treatment with Fludarabine for Patients with Follicular and other Low Grade Non-Hodgkin's Lymphoma and Waldenstrom's Macroglobulinemia Practice Guideline Report #6-2

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SUMMARY

Guideline Questions

1. What are the relative efficacy and other benefits of fludarabine compared with alternative options when treating patients with advanced-stage follicular and other low grade lymphoma and Waldenstrom's Macroglobulinemia? Outcomes of interest include overall survival, progression-free survival, quality of life, and economic evaluations.
2. What are the toxicities of fludarabine?

Target Population

These recommendations apply to adult patients with stage III-IV follicular and other low grade lymphoma or Waldenstrom's Macroglobulinemia who require therapy. Patients who require initial therapy, or who have been previously treated, are considered.

Recommendations

Previously Untreated Patients with Stage III-IV Low Grade Lymphoma

- There is insufficient evidence to support the use of fludarabine as initial therapy in these patients. Other therapies such as chlorambucil with or without prednisone; cyclophosphamide, vincristine, and prednisone; or cyclophosphamide, doxorubicin, vincristine, and prednisone should be considered as first-line therapy, with the choice of treatment determined by patient preferences and clinical judgement. Choice of treatment should take into account factors such as route of administration, risk of infection, and outcomes of interest.

Previously Treated Patients with Stage III-IV Low Grade Lymphoma

- Fludarabine is an acceptable option for patients requiring treatment following disease progression after first-line therapy. Other therapies such as chlorambucil with or without prednisone; cyclophosphamide, vincristine, and prednisone; cyclophosphamide, doxorubicin, vincristine, and prednisone; or rituximab may be appropriate alternatives. Choice of treatment should be determined by patient preferences, clinical judgement, and drug availability and should take into account factors such as the route of administration, the risk of infection, and outcomes of interest.

Patients with Waldenstrom's Macroglobulinemia

- There is insufficient evidence to support the use of fludarabine as initial therapy in these patients.

- Fludarabine is an acceptable option for patients previously treated with alkylator-based therapy who have relapsed or refractory disease.

Qualifying Statements

- Although the incidence of serious infections has been shown to be similar between patients treated with fludarabine and the combination of cyclophosphamide, vincristine, and prednisone, fludarabine significantly depresses T-cell-mediated immunity. Prophylaxis against pneumocystis carinii pneumonia with cotrimoxazole should be considered.
- Autoimmune hemolytic anemia, a condition associated with lymphoma, may be exacerbated or precipitated by fludarabine and is considered by the manufacturer as a contraindication to the use of this drug.
- The Canadian Blood Services and the British Committee for Standards in Hematology Blood Transfusion Task Force recommend that patients receiving, or who have previously received, fludarabine should receive gamma-irradiated blood products because of the risk of transfusion-related graft-versus-host disease.
- Standard therapy with fludarabine consists of 25 mg/m² per day given intravenously for five consecutive days, for a total of six cycles, 28 days apart, or two cycles beyond maximum response.

Methods

Entries to MEDLINE (1985 through June 2001), CANCERLIT (1985 through March 2001), and Cochrane Library (1999 through Issue 2, 2001) databases and abstracts published in the proceedings of the annual meetings of the American Society of Hematology (1997-2000) and the American Society of Clinical Oncology (1997-2001) were systematically searched for evidence relevant to this practice guideline report. In addition, the Physician's Data Query clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) and PUBMED were searched.

Evidence was selected and reviewed by two members of the Practice Guidelines Initiative's Hematology Disease Site Group and methodologists. This practice guideline report has been reviewed and approved by the Hematology Disease Site Group, which is comprised of hematologists, medical oncologists, radiation oncologists, methodologists, and a patient representative.

External review by Ontario practitioners for all reports was obtained through a mailed survey. Final approval of all reports was obtained from the Practice Guidelines Coordinating Committee (PGCC).

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Key Evidence

- Fludarabine has been compared with the combination of cyclophosphamide, doxorubicin, teniposide, and prednisolone, plus interferon, in a randomized trial involving 131 previously untreated patients ages 60-75 years, with follicular lymphoma and at least one high-risk feature. Patients receiving fludarabine had an inferior two-year time to treatment failure (49% versus 63%, p<0.05) and two-year survival (62% versus 77%, p<0.05).
- Fludarabine has been compared with the combination of cyclophosphamide, vincristine, and prednisone in a randomized trial reported in preliminary abstract form involving 309 previously untreated patients with diffuse small lymphocytic and follicular small cleaved or mixed cell lymphoma. Respective median progression-free survivals were 494 and 396

days (p value not given). Too few events had occurred to allow for an assessment of overall survival.

- Fludarabine has been compared with the combination of cyclophosphamide, vincristine, and prednisone in a randomized trial reported in preliminary abstract form involving 91 patients with low grade lymphoma who had previously received one to four treatment regimens. Patients receiving fludarabine had a superior two-year progression-free (32% versus 14%; p=0.028) and two-year treatment-free survival (41% versus 20%; p=0.034). No difference in two-year overall survival was detected (70% versus 75%; p=0.738). This study also assessed quality of life and demonstrated superior social function in patients receiving fludarabine.
- Fludarabine has been compared with the combination of cyclophosphamide, doxorubicin, and prednisone in a randomized trial reported in preliminary abstract form involving 92 patients with Waldenstrom's Macroglobulinemia who were either refractory to or relapsed from initial alkylator-based therapy. Response was superior in patients receiving fludarabine (28% versus 11%; p=0.019). Superior progression-free survival in responding patients (p=0.02) and treatment-free survival in all patients (p=0.04) were also observed with fludarabine. No difference in survival was detected. Fludarabine was associated with less mucositis and alopecia; no differences in other toxicities were detected. Using a Q-TWiST analysis, patients receiving fludarabine spent more time without symptoms of disease or treatment toxicity (5.9 months; p=0.006).

Related Guidelines

The Practice Guidelines Initiative's:

- Practice Guideline Report #6-1: *Fludarabine in Intermediate- and High-risk Chronic Lymphocytic Leukemia*.
- Evidence Summary Report #6-8: *Rituximab in Lymphoma*.

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*The Practice Guidelines Initiative is sponsored by:
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PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.¹ The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee (PGCC), whose membership includes oncologists, other health providers, patient representatives, and Cancer Care Ontario executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:

¹ Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

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