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Rituximab (Mabthera) for follicular non-Hodgkin's lymphoma-first line maintenance therapy

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Rituximab (Mabthera) for follicular non-Hodgkin's lymphoma-first line maintenance therapy

Target group

- Non-Hodgkin's follicular lymphoma (NHL) - first line maintenance therapy after first line induction chemotherapy (with or without rituximab).

Background

Non-Hodgkin’s lymphomas (NHLs) are malignant tumours of the lymphoid system that usually manifest by enlargement of the lymph nodes throughout the body. The disease gives rise to generalised symptoms such as malaise, weight loss, fevers and night sweats, as well as local pain and restriction in movement associated with enlarged lymph nodes. There are a number of well-known risk factors for NHLs including infectious agents, immunosuppression, genetic susceptibility and occupational exposures. The NHLs are traditionally divided into 2 prognostic groups:

- Indolent or low-grade lymphomas with a long median survival. The majority of lymphomas, including follicular lymphoma (FL), fall into this group. They are currently incurable at advanced stages with a median survival of 8 to 10 years.
- Aggressive or high-grade lymphomas. These have a short natural history and a 50-60% cure rate.

NHL is staged (stages I to IV) by how widely dispersed affected lymph nodes and extra-lymphatic disease are around the body.

Technology description

Rituximab (MabThera) is a genetically engineered, humanised monoclonal IgG antibody to the CD20 antigen present on the cell surface of normal human B-lymphocytes and malignant cells derived from them, including B-cell lymphomas and B-cell chronic lymphocytic leukaemias. After binding to the CD20 antigen, rituximab is believed to exert its therapeutic effect by promoting B-cell lysis.

It is intended that rituximab will be used after standard first line treatment induction therapy for NHL (chemotherapy with or without rituximab). In trials the schedule used is 375 mg/m^2 body surface area intravenously (iv), every 8 weeks for 24 months.

Rituximab currently has an EU Marketing Authorisation in NHL for:

- Previously untreated stage III-IV follicular lymphoma in combination with chemotherapy;
- Maintenance therapy for patients with relapsed or refractory follicular lymphoma responding to induction therapy with chemotherapy with or without rituximab;
- Monotherapy for treatment of Stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy;
- CD20 positive diffuse large B-cell NHL in combination with cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) chemotherapy.

Rituximab is in phase III clinical trials for chronic lymphocytic leukaemia.

Innovation and/or advantages

Results from a phase III trial show that rituximab maintenance increased progression free and overall survival compared to observation alone.

Developer

Roche Products Ltd.

Place of use

- ☐ Home care e.g. home dialysis
- ☐ Community or residential care e.g. district nurses, physio
- ☐ Primary care e.g. used by GPs or practice nurses
- ☑ Secondary care e.g. general, non-specialist hospital
- ☑ Tertiary care e.g. highly specialist services or hospital
- ☐ Emergency care e.g. paramedic services, trauma care
- ☐ General public e.g. over the counter
- ☐ Other:

Availability, launch or marketing dates, and licensing plans:

In phase III clinical trials.

NHS or Government priority area:

This topic is relevant to the NHS Cancer Plan

Relevant guidance

- NICE cancer service guideline. Haemato-oncology. October 2003[1].
- NICE technology appraisal. Rituximab for the treatment of follicular lymphoma. 2006[2].
- NICE technology appraisal. Rituximab for aggressive non-Hodgkin's lymphoma. 2003[3].
- NICE technology appraisal. Rituximab for recurrent or refractory stage III or IV follicular non-Hodgkin's lymphoma. 2002 (expected review in February 2008)[4].

Clinical need and burden of disease

NHL represents approximately 4% of all cancers diagnosed in the UK, with 8,841 new cases registered in England and Wales in 2005 and 3,929 registered deaths[5]. Indolent lymphomas, the majority of which are FL, make up 30-35% of all NHL subtypes (approximately 2,652 - 3,094 cases)[6].

Existing comparators and treatments

There are several management options used in sequence including:

- Watching and waiting whilst the disease remains stable and the patient symptom free;
- Single agent chemotherapy such as chlorambucil with or without steroids, or rituximab;
- Combination chemotherapy such as CHOP with or without additional agents such as fludarabine or rituximab (R-CHOP);
- Other therapies such as cladribine and interferon.

Disease remissions characteristically become shorter with each successive treatment. Early stage disease (stages I and II) can be treated with radiation limited to the site of the lymphoma and adjacent areas, extending survival by 5 to 8 years.

Efficacy and safety

Trial name	ECOG 1496; phase III.	PRIMA EUDRACT 2004-001756-36; Phase III.	MAXIMA.
Sponsor	Eastern Co-operative Oncology Group (ECOG)	GELA and CTAAC[a]	Roche
Status	Published[7,8]	Ongoing	Ongoing
Location	Europe	Europe and Australia	International
Design	Randomised	Open-label, randomised, controlled	Uncontrolled, non-randomised, open-label
Participants	n=305; advanced indolent NHL (78% stage III/IV) achieving partial remission (PR), complete remission (CR) or stable disease following CVP induction chemotherapy. Randomised to rituximab maintenance (4 weekly doses repeated at 6 monthly intervals for up to 2 years) or observation.	n=1,200; confirmed FL grade I, II or IIIa; previously untreated. Induction with R-CVP, R-CHOP or R-FCM (rituximab, fludarabine, cyclophosphamide, and mitoxantrone); then rituximab 375 mg/m^2 every 8 weeks for 24 months (12 infusions) or control with no treatment.	n=500; confirmed follicular lymphoma grade I, II or IIIa; rituximab containing induction regimen, first-line or relapsed disease. All patients receive rituximab 375mg/m^2, every 8 weeks.
Follow-up	3 years	2 years	1-2 years.
Primary outcome	Progression free survival (PFS), overall survival (OS)	PFS and OS	Safety and efficacy.
Secondary outcomes	-	Event-free survival (EFS), OS, time to next lymphoma treatment (TTNLT), time to next chemotherapy, response, transformation and quality of life.	PFS, EFS, OS, TTNLT, PR to CR conversion rate.
Key results	At median follow-up of 3 years, overall PFS was 4.2 vs 1.5 years for rituximab vs observation (p=0.00003). Subgroup analysis of 237 patients with FL found median PFS of 61 vs 15 months for rituximab and observation ($p=3x10^{-7}$; HR = 0.4). OS at 48 months was 91% vs. 75% for rituximab vs observation (p=0.03; HR = 0.5).	-	-
Adverse effects	Rituximab was generally well-tolerated; no significant increase in neutropenia, thrombocytopenia or infection.	-	-

Estimated cost and cost impact

A maintenance regimen of rituximab over 2 years at 375 mg/m^2 for 12 doses would cost £14,669 per patient[b].

[a] Groupe d'Etude des Lymphomes de l'Adulte (GELA) and Clinical Trials Advisory and Awards Committee (CTAAC).

Potential or intended impact – speculative

The administration of rituximab for maintenance would entail additional clinic visits for the 2-monthly infusions. Infusion of rituximab typically takes several hours and additional costs include the preparation of the infusion and use of steroid and antihistamine premedications to prevent rituximab-associated infusion reactions.

Patients

☑ Reduced morbidity
☑ Reduced mortality or increased survival
☑ Improved quality of life for patients and/or carers
☐ Quicker, earlier or more accurate diagnosis or identification of disease
☐ Other:
☐ Non identified

Services

☑ Increased use e.g. length of stay, out-patient visits
☐ Service reorganisation required
☐ Staff or training required
☐ Decreased use
☐ Other:
☐ Non identified

Costs

☐ Increased unit cost compared to alternative
☐ Increased costs: more patients coming for treatment
☐ Increased costs: capital investment needed
☑ New costs:
☐ Savings:
☐ Other:

References

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[b] BNF 54. September 2007 average patient 1.7 m^2

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