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Lenalidomide (Revlimid) in combination with rituximab for untreated follicular lymphoma

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LAY SUMMARY

Lymphoma is a cancer of the lymphatic system. Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) are the two main types of lymphoma, with the latter being more common. Follicular lymphoma is a type of NHL that usually grows slowly, going through remission and relapse, and is more common in people aged over 60.

Lenalidomide is a drug, administered as a tablet, which affects the activity of the immune system and may impact the growth and spread of cancer cells. An ongoing phase III clinical trial explores whether offering it together with rituximab (an antibody) could be a viable therapy option for patients who have not had any prior treatment for their follicular lymphoma. Currently most of these patients would receive rituximab in combination with chemotherapy.

TARGET GROUP

Follicular lymphoma: untreated – first line; in combination with rituximab

TECHNOLOGY

DESCRIPTION

Lenalidomide (Revlimid; CDC-5013) is a class I thalidomide analogue, an immunomodulatory drug (IMiD) with immune, anti-angiogenic, and direct anti-lymphoma effects.[1] Class I IMiDs are broad inhibitors of LPS-induced inflammatory cytokines.[2] Follicular lymphoma cells produce a specific defect in the immune system impairing cancer control, which lenalidomide has been shown to reverse.[3] By blocking angiogenesis, the development of new blood vessels, lenalidomide impacts the growth and spread of cancer cells.[4]

Rituximab-chemotherapy combination (e.g. R-CHOP) is the standard first-line treatment for follicular lymphoma,[5] but adding biologic agents with alternative mechanisms of action (such as cytokines, other antibodies, and immunomodulatory or proapoptotic agents) to the treatment regimen has been explored for their potential additive activity and lower toxicity.[1]

In a phase III trial in patients with untreated follicular lymphoma, lenalidomide was administered orally, with a 20mg dose on days 2-22 for six 28-day cycles, in combination with rituximab.[3] If there is a complete response, 10mg was administered on days 2-22 every 28 days for 12 cycles. If there is a partial response after six cycles, a 20mg dose was continued for three to six cycles and then 10mg on days 2-22 for up to 18 cycles.

Lenalidomide is already licensed in the EU for multiple myeloma, myelodysplastic syndromes and mantle cell lymphoma.[6] The company indicates that more than 500,000 patients have been exposed to lenalidomide worldwide and its safety profile is well characterized in approved indications. The Electronic Medicines Compendium lists hypothyroidism (overproduction of thyroid hormone) as the most commonly reported adverse effect reported in post-marketing use; other adverse effects of unknown frequency include viral infections, acquired haemophilia, acute hepatic failure, hepatitis toxic, cytolytic hepatitis, cholestatic hepatitis, mixed cytolytic/cholestatic hepatitis.[7]

Lenalidomide is currently in phase III clinical trials for follicular lymphoma, marginal zone lymphoma and diffuse large B-cell lymphoma.[8] It was approved for Adult T-cell Leukaemia-Lymphoma (ATLL) in early 2017 in Japan.

INNOVATION and/or ADVANTAGES

If licensed for this indication, lenalidomide in combination with rituximab may offer an additional first-line treatment option for patients with follicular lymphoma. Lenalidomide combination treatment has the potential to improve anti-tumour and immune response in patients.

DEVELOPER

Celgene Ltd

AVAILABILITY, LAUNCH or MARKETING

Lenalidomide is a designated orphan drug in the EU[9] and USA[10] for follicular lymphoma.

PATIENT GROUP

BACKGROUND

Follicular lymphoma is the most common type of low-grade non-Hodgkin's lymphoma.[11] It grows slowly, developing from B lymphocytes, with the abnormal lymphocytes collecting in lymph nodes in clumps known as 'follicles'.[11] Symptoms of follicular lymphoma typically include painless, swollen lymph nodes in the neck, armpit or groin.[5] Systemic symptoms (such as fever, fatigue, night sweats, and unexplained weight loss) are rare.[5]

Follicular lymphoma is classified into four stages of disease (I–IV) reflecting the number of sites involved in the disease and presence above/below the diaphragm.[5] Majority of people present at an advanced stage of disease (III–IV). A clinical course of remission and relapse is characteristic of the disease, and advanced follicular lymphoma is incurable.[5] Treatment aims to increase life expectancy and quality of life, and a NICE technology appraisal notes that increased median survival times have been reported in the past decade.[5]

CLINICAL NEED and BURDEN OF DISEASE

There were 11,620 new cases of non-Hodgkin's lymphoma in England in 2014.[12] For follicular lymphoma, the Haematological Malignancy Research Network estimates an annual rate of incidence of 3.3 per 100,000 in the UK, with an expected 1,900 new cases per year.[13]

More than 70% of follicular lymphomas are diagnosed in people aged over 60 years (NICE TA), and the median age at diagnosis is 65.[14] Five-year survival rate of patients diagnosed with follicular lymphoma is 87.2%.[14] Cancer Research UK notes that 90% of patients diagnosed at stage I or II survive ≥5 years, and this reduces to 80% in patients diagnosed at stage III or IV.

In 2015-16, there were 22,668 admissions for follicular lymphoma, resulting in 12,933 bed days and 23,325 finished consultant episodes in England.[15]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Lymphoma (follicular, rituximab-refractory) - obinutuzumab (with bendamustine) [ID841]. Expected date of issue to be confirmed.
- NICE technology appraisal in development. Obinutuzumab for untreated advanced follicular lymphoma [ID1020]. Expected January 2018.

- NICE technology appraisal. Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma (TA306). February 2014.
- NICE technology appraisal. Rituximab for the first-line treatment of stage III-IV follicular lymphoma (TA243). January 2012.
- NICE technology appraisal. Rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma (TA226). June 2011.
- NICE technology appraisal. Rituximab for the first-line treatment of chronic lymphocytic leukaemia (TA174). July 2009.
- NICE technology appraisal. Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma (TA137). February 2008.
- NICE technology appraisal. Rituximab for aggressive non-Hodgkin's lymphoma (TA65). September 2003.

- NICE guideline. Non-Hodgkin's lymphoma: diagnosis and management (NG52). July 2016.
- NICE guideline. Haematological cancers: improving outcomes (NG47). May 2016.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Children, Teenagers and Young Adults). B12/S/b.
- NHS England. 2013/14 NHS Standard Contract for Haematopoietic Stem Cell Transplantation (Adult). B04/S/a.

- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation. NHSCB/B04/P/a. April 2013.
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT) (All Ages): B04/P/a. Revised January 2015.

OTHER GUIDANCE

- Dreyling M, Ghielmini M, Rule S, et al. (2016) Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 27 (Suppl 5): v83-v90. Available at: http://www.esmo.org/Guidelines/Haematological-Malignancies/Newly-Diagnosed-and-Relapsed-Follicular-Lymphoma
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- British Committee for Standards in Haematology. Best practice in lymphoma diagnosis and reporting. 2010.

CURRENT TREATMENT OPTIONS

If follicular lymphoma is diagnosed at stage IIA, before symptoms develop, watchful waiting is the usual course of action.[16] NICE recommends rituximab induction therapy for asymptomatic patients

at stages III-IV.[16] For symptomatic patients requiring first-line systemic therapy, the recommended treatment is rituximab (a monoclonal antibody) and chemotherapy (most commonly CVP or CHOP). Patients on a lower performance status may receive single-agent chemotherapy (chlorambucil).[16]

After first-line treatment, rituximab is recommended as maintenance treatment. Once the disease relapses, treatment is determined depending on what first-line treatment was used, duration of response and any transformation.[5 16]

EFFICACY and SAFETY

Trial	RELEVANCE, NCT01650701 and NCT01476787, RV-FOL-GELARC-0683 and RV-FOL-GELARC-0683C, combined rituximab and lenalidomide vs rituximab and chemotherapy; phase III.
Sponsor	Lymphoma Academic Research Organisation, Celgene
Status	ongoing
Source of Information	Trial registry entries,[3 17] company
Location	EU (not UK), USA, Canada and other countries
Design	Randomised, open-label, parallel-assignment
Participants	N=1,000; RV-FOL-GELARC-0683 (N=750) and RV-FOL-GELARC-0683C (N=250); aged ≥18 years; histologically confirmed follicular lymphoma grade 1, 2 or 3a, Stage II-IV; no prior systemic treatment for lymphoma
Schedule	Patients randomized to receive rituximab-lenalidomide will receive six cycles of lenalidomide 20mg daily on days 2-22 every 28 days. Patients exhibiting a complete response (CR/Cru) after six cycles then receive 12 cycles of 10 mg lenalidomide daily on days 2-22 every 28 days for a total of 18 cycles. Patients exhibiting a partial response (PR) after six cycles receive an additional 3 or 6 cycles of the 20 mg lenalidomide dose until they achieve a CR/CRu at which time they receive the 10 mg lenalidomide dosing for 9 or 6 cycles respectively for a total of 18 cycles. Patients who remain in PR after the additional 6 cycles will receive 10 mg lenalidomide dosing for a total of 18 cycles. Comparators: R-CHOP, R-CVP, R-Bendamustine
Follow-up	Primary endpoint at 120 weeks. Follow-up: up to 13 years.
Primary Outcomes	Complete response rate, progression-free survival, safety
Secondary Outcomes	Adverse events, time to treatment failure, event free survival, time to next anti-lymphoma treatment, overall survival, health-related quality of life
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as May 2017.

Trial	CALGB-50803; NCT01145495; phase II trial
Sponsor	National Cancer Institute
Status	published
Source of Information	Trial registry,[18] publication abstract[19]
Location	USA
Design	Non-randomised, uncontrolled interventional single group trial
Participants	N=63; aged ≥18 years; median age 53; 34 female; previously untreated, histologically confirmed follicular lymphoma; stage III, IV, or bulky stage II
Schedule	Lenalidomide 20 mg PO QD on days 1-21. 28-day cycles for 12 courses in the absence of disease progression or unacceptable toxicity. Patients also receive 375 mg/m2 rituximab IV on days 1, 8, 15, and 22 and in weeks 13, 21, 29, and 37 in the absence of disease progression or unacceptable toxicity.
Follow-up	Up to 10 years
Primary Outcomes	Number of participants who achieved a complete response (CR)
Secondary Outcomes	Toxicity of study treatment, time to disease progression, time to best response
Key Results	50 patients completed 12 cycles of lenalidomide. The overall RR in evaluable subjects was 93% (53/57); the CR rate was 72%. The median time to CR was 10 weeks and 92% of PET-negative CRs occurred by 24 weeks. With a median follow-up of 2.3 years, the 2-year PFS is 89%.
Adverse effects (AEs)	Grade 3-4 hematologic toxicity included neutropenia (19%), lymphopenia (8%), and thrombocytopenia (2%). Febrile neutropenia occurred in 1 pt. Grade 3-4 non-hematologic toxicity occurring in at least 2 pts included rash (8%), infection (8%), pain (8%), fatigue (6%), tumor lysis (3%).
Expected reporting date	-

ESTIMATED COST and IMPACT

COST

The cost of lenalidomide for this indication is not yet known.

However, lenalidomide is already licenced in the UK for the treatment of multiple myeloma and myelodysplastic syndromes. The cost for lenalidomide capsules is cited in the BNF as: 10 mg (blue/yellow), 21-cap pack = £3780.00; 15 mg (pale blue/white), 21-cap pack = £3969.00; 25 mg (white), 21-cap pack = £4368.00.[20]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS and CARERS

☐ Reduced mortality/increased length of survival ☒ Reduced symptoms or disability

☐ Other ☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services ☐ Decreased use of existing services

☐ Re-organisation of existing services ☐ Need for new services

☐ Other ☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs ☐ Reduced drug treatment costs

☐ Other increase in costs ☐ Other reduction in costs

☒ Other: *uncertain unit cost for the new indication* ☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified: *specify* ☒ None identified

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