Horizon Scanning in Oncology

Rituximab (Rituxan®/MabThera®) for the first- and second-line treatment of chronic lymphocytic leukaemia

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Author(s):	Dr. Marisa Warmuth; MIPH
Internal Review:	Dr. Anna Nachtnebel; MSc
	Dr. Claudia Wild
External Review:	Dr. Wolfgang Willenbacher, Innsbruck University Hospital, Dep. Haematology & Oncology

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CONTACT INFORMATION

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Responsible for Contents:

Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA)
Garnisongasse 7/20, A-1090 Vienna
http://hta.lbg.ac.at/

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1 Drug description

Generic/Brand name:

Rituximab/Rituxan® (United States, Japan, Canada), MabThera® (rest of the world)

Developer/Company:

Genentech, Inc., and Biogen Idec. co-market MabThera in the United States. Chugai Pharmaceutical and Zenyaku Kogyo Co. Ltd. co-market MabThera in Japan. Hoffmann-La Roche Ltd. markets MabThera in the rest of the world [1].

Description:

Rituximab belongs to the pharmacotherapeutic group of antineoplastic agents and monoclonal antibodies (ATC code: L01XC02) [2].

rituximab induces lysis and apoptosis of normal and malignant human B-cells by binding to the CD20 antigen

Rituximab is a chimeric murine/human anti-CD20 monoclonal antibody targeted against the cluster of differentiation (CD) 20 antigen expressed on the surface of human B-cells. By binding to the CD20 antigen it promotes antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity and induces lysis and apoptosis of normal and malignant human B- cells. Furthermore, it sensitises malignant B-cells to the cytotoxic effect of chemotherapy [3, 4].

six cycles of combination therapy of fludarabine, cyclophosphamide, and rituximab

The recommended treatment regimen consists of six treatment cycles of rituximab in combination with fludarabine and cyclophosphamide at intervals of 28 days (= 1 cyle). Rituximab is administered only once at the beginning of every cycle with an initial starting dose of 375mg/m^2 body surface area (BSA) intravenously (IV) (Cycle 1), followed by 500mg/m^2 IV (Cycle 2-6) [2].

hydration, uricostatics, and prednisone are recommended to prevent a cytokine release syndrome

Prior to start of therapy precautions, such as ensuring adequate hydration and administration of uricostatics, are recommended to reduce the risk of tumour lysis syndrome. In addition, for CLL patients whose lymphocyte counts are more than 25 x 10^9/L prednisone/prednisolone 100mg IV should be administered shortly before infusion of rituximab to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome [2].

dyspnoea, bronchospasm, hypoxia may be symptoms of a cytokine release syndrome

Patients have to be monitored closely for onset of a cytokine release syndrome (CRS) with severe reactions, such as severe dyspnoea, bronchospasm or hypoxia, which require intermediate interruption of infusion. If symptoms resolve, the infusion of rituximab may be restarted at half of the previous rate [2].

2 Indication

Rituximab is indicated for the first-line treatment of patients with chronic lymphocytic leukaemia (CLL) in combination with chemotherapy [2].

3 Burden of disease

CLL is the most common leukaemia in industrialised countries, and affects mainly men aged ≥70 years

Chronic lymphocytic leukaemia (CLL) belongs to the entity of indolent B-cell non-Hodgkin lymphomas (NHL) and is the most common adult leukaemia in the Western World. It accounts for 40% of all leukaemias in individuals aged more than 65 years with men being affected twice as often as women. The median age of presentation is 70 to 74 years [5].

Risk factors for developing CLL include older age, male sex, white ethnicity, family history of CLL or other blood and bone marrow cancers and exposure to certain chemicals, such as herbicides and insecticides [6].

the majority of patients is asymptomatic at diagnosis; symptoms may be lymphadenopathy and "B" symptoms

In the majority of cases CLL is diagnosed incidentally by routine complete blood count examination. Most patients are asymptomatic at the time of diagnosis. The most common symptom is lymphadenopathy, followed by so called "B" symptoms, including fever, night sweats and weight loss. The life expectancy of patients with early stage disease at diagnosis is greater than ten years but decreases with advanced disease at diagnosis to a median survival of less than one year [7-9].

diagnosis requires B lymphocytosis ≥5.0 x 10^9/L in the peripheral blood for ≥ 3 months

According to the recently updated National Cancer Institute-Working Group 1996 guidelines for the diagnosis and treatment of chronic lymphocytic leukaemia [10], the diagnosis of CLL requires a B lymphocytosis of ≥5.0 x 10^9/L with characteristic morphology and immunophenotype in the peripheral blood for at least three months [5, 10]. Interphase fluorescence-in situ hybridization (FISH) is recommended at diagnosis to identify cytogenetic lesions, such as deletion in the short arm of chromosome 17 (del(17p)) which is associated with resistance to standard chemotherapy regimens and poor prognosis [10].

clinical staging depends on standard laboratory tests and physical examination

There are two classification systems for the clinical staging of CLL, depending on standard laboratory tests and physical examination, including the Rai classification and the Binet staging system. The Rai classification distinguishes low (formerly Rai stage 0), intermediate (formerly Rai stage I or II) and high (formerly Rai stage IV and V) risk disease, whereas the Binet staging is subdivided into stage A, B and C [10].

advanced disease stage, short lymphocyte doubling time, etc. worsen the prognosis

The prognosis of CLL depends upon several factors und might be worsened by advanced disease stage, short lymphocyte doubling time, higher levels of beta-2-microglobulin, absence of immunoglobulin variable region heavy chain mutation, ZAP-70 (zeta-chain associated protein kinase 70) positivity, FISH chromosomal abnormalities and CD38 positivity [11].

Standard treatment options for patients with CLL comprise watchful waiting, radiation therapy, chemotherapy, corticosteroids, and monoclonal antibody therapy [11].

The initiation of treatment is not recommended for asymptomatic early-stage disease (Rai 0, Binet A). In these patients a watch-and-wait strategy with controls of blood cell counts and clinical examination every three to six months is recommended until there is evidence of disease progression. In patients with intermediate and high risk disease, according to the Rai classification as well as patients with Binet stage B or C disease, the initiation of treatment is recommended, whereas some patients with intermediate disease or Binet stage B might as well be monitored until disease progresses [9, 10]. Disease progression requiring treatment is based on certain criteria, such as increasing adenopathy, hepatosplenomegaly, development of auto-immune cytopenias, and marrow failure [5, 10].

initiation of treatment depends on clinical staging; adenopathy, hepatosplenomegaly, autoimmune cytopenias, and marrow failure require treatment

Overall, the incidence of CLL seems to depend on the ethnicity with white males having the highest incidence of CLL of 6/100,000/year (y), followed by white females with an incidence of 3.1/100,000/y [12].

highest incidence of CLL in Whites

In Austria the overall incidence of all forms of leukaemia (C91-C95[1] according to the World Health Organization's International Classification of Diseases - 10 [13] was 7.3/100,000/y in 2006. Among males, the incidence was 8.6/100,000/y, whereas among females it was 6.3/100,000/y in 2006. The overall death rate of all forms of leukaemia was 4.6/100,000/y in Austria in 2006. Within men, the death rate was 5.9/100,000/y and within women it was 3.7/100,000/y in 2006 [14].

In the United States the age-adjusted incidence of chronic lymphocytic leukaemia in Whites was 6.23/100,000/y in males and 3.49/100,000/y in females in 2006 [12].

The incidence of CLL in Austria is expected to rise in the future due to an increasing elderly stratum of the population.

incidence of CLL in Austria is increasing

4 Current treatment

There are various treatment options for CLL depending on disease stage, patient's age, presence of cytogenetic lesions, concomitant diseases and – with second line therapy – duration of response, including (ordered from the least to the most toxic options) [11]

several treatment options for first- and second-line therapy

- Observation/watchful waiting

[1] C91 = Lymphoid leukaemia + subtypes, one of which is CLL (C91.1); C92 = Myeloid leukaemia + subtypes; C93 = Monocytic leukaemia + subtypes; C94 = Other leukaemias of specified cell type + subtypes; C95 = Leukaemia of unspecified cell type + subtypes

observation,

chemotherapy,

chemoimmunotherapy,

involved-field radiation therapy,

radioimmunotherapy,

anti-CD52 monoclonal antibody,

bone marrow and peripheral stem cell transplantation

- Oral alkylating agents (chlorambucil) with or without corticosteroids
- Purine analogs (fludarabine, 2-chlorodeoxyadenosine, pentostatin)
- Combination chemo(immuno)therapy (e.g. fludarabine + cyclophosphamide (FC), cyclophosphamide + vincristine + prednisone (COP), cyclophosphamide + doxorubicin + vincristine + prednisone (CHOP), fludarabine + cyclophosphamide + mitoxantrone (FCM), bendamustine, besides others)
- Involved-field radiation therapy
- Radioimmunotherapy
- Anti-CD52 monoclonal antibody (alemtuzumab)
- Bone marrow and peripheral stem cell transplantations are currently under clinical evaluation in patients younger than 60 years with adverse prognostic factors

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology [15] provide detailed information on current treatment options for both first- and second-line therapy of CLL.

5 Current regulatory status

EMEA approval for the first-line treatment of CLL; non-Hodgkin lymphomas; rheumatoid arthritis

Rituximab (MabThera®) was approved by the European Medicines Agency (EMEA) [2]

- for the first-line treatment of patients with CLL in combination with chemotherapy in January 2009.
- for the treatment of NHL (first approval was granted in 1998 with subsequent extensions of indication), including
  - previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy.
  - maintenance therapy of patients with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without rituximab.
  - monotherapy of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.
  - patients with CD20-positive, diffuse large B-cell NHL in combination with cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) chemotherapy.
- in combination with methotrexate for adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs including one or more tumour necrosis factor inhibitor therapies in June 2006.

In addition, the Committee for Medicinal Products for Human Use of the EMEA adopted a positive opinion to recommend MabThera® in combination with chemotherapy for the treatment of patients with relapsed/ refractory CLL in July 2009 [2].

EMEA issued a positive opinion concerning second-line therapy of CLL with rituximab

In Austria off-label use of rituximab include refractory autoimmune cytopenias, such as autoimmune haemolytic anaemia and idiopathic thrombocytopenic purpura, as well as treatment of complications related to transplantation, such as rejection reaction, Graft-versus-host-disease, and post-transplant lymphoproliferative disorder, besides others.

off-label use in Austria for autoimmune cytopenias, complications of transplantation, besides others

Rituximab (Rituxan®) was approved by the United States Food and Drug Administration (FDA) [16]

- for the treatment of NHL, including
  - relapsed/ refractory low-grade or follicular CD20-positive, B-cell NHL as a single agent in November 1997.
  - previously untreated follicular, CD20-positive, B-cell NHL in combination with cyclophosphamide, vincrinstine, prednisolone (CVP) chemotherapy in September 2006.
  - non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line CVP chemotherapy in September 2006.
  - previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens in October 2006.
- in combination with methotrexate to reduce the signs and symptoms in adult patients with moderately - to severely - active rheumatoid arthritis who have had an inadequate response to one or more tumour necrosis factor antagonist therapies in February 2006.

FDA approval for non-Hodgkin lymphomas and rheumatoid arthritis

In addition, the manufacturers submitted two supplemental Biologics License Applications to FDA concerning treatment with rituximab in combination with standard chemotherapy for patients with previously treated or untreated lymphocytic leukaemia in May 2009 [17].

FDA supplemental Biologics License Applications for first- and second-line treatment of CLL

6 Evidence

To date, no randomised controlled trials concerning the first- and second-line treatment of CLL with rituximab, fludarabine and cyclophophamide (FCR) have been fully published in peer-reviewed journals [18]. Nevertheless, there are two completed phase III trials (as shown in section 6.1) which assessed the combination of FCR compared to fludarabine and cyclophosphamide (FC) in patients with both previously untreated, active CLL and patients with relapsed or refractory CLL [19]. The results of these two trials were initially presented at the American Society of Hematology annual meeting in December 2008. In addition, several phase II trials (described in

two phase III studies were conducted concerning the first- and second-line treatment of CLL with rituximab in combination with chemotherapy but have not been published in peer-reviewed journals

section 6.2) have assessed the combination of FCR in the first- and second-line treatment of CLL.

CLL is biologically and clinically heterogeneous

Overall, it is important to note that the biologic and clinical heterogeneity of CLL makes it difficult to compare and extrapolate the results of clinical trials [20].

6.1 Efficacy and safety - Phase III studies

Table 1: Phase III studies of rituximab for the first- and second-line treatment of CLL

Reference	CLL-8 / ML17102 Protocol of the German CLL Study Group (GCLLSG) – completed, to be published [2, 19, 21-24] EUDRACT-2004-004938-14 ISRCTN02757147 NCT00281918	REACH trial / BO17072 – completed, to be published [19, 21, 25, 26] NCT00090051
Sponsor	Hoffmann-La Roche Ltd, Basel, Switzerland	Biogen Idec. Collaborators: Hoffmann-La Roche, Genentech
Country	Multicentre – International (190 study sites across 11 countries)	Multicentre – International (88 study sites across 17 countries)
Design	Prospective, randomised, open-label, active control (Randomisation stratified by country and disease stage according to the Binet staging system), crossover (patients with stable disease or progressive disease after three cycles of treatment were withdrawn from study treatment and eligible to receive alternative treatment, including rituximab-containing regimens)	Randomised, open-label , active control
Participants characteristics	n=817 patients (pts) (I: 408 vs. C: 409); median age I: 61y (30-80y), C: 61y (36-81y);	n=552 patients (pts) (I:276 vs. C:276); median age I: 63y (35-83y), C: 62y (35-81y);
Treatments	I(ntervention): Rituximab +Fludarabine + Cyclophosphamide for a total of six treatment cycles at intervals of 28 days Rituximab IV infusion before FC infusion Cycle 1: 375mg/m² IV; do Cycle 2-6 : 500mg/m² IV ; d1 Fludarabine IV infusion over three days for six treatment cycles (25mg/m²/day IV; d1-d3) Cyclophosphamide IV infusion over three days for six treatment cycles (250mg/m²/day IV; d1-d3) C(ontrol): Fludarabine + Cyclophosphamide Fludarabine IV infusion over three days for six treatment cycles (25mg/m²/day IV; d1-d3) Cyclophosphamide IV infusion over three days for six treatment cycles (250mg/m²/day IV; d1-d3)	I(ntervention):Rituximab + Fludarabine + Cyclophosphamide for a total of six treatment cycles at intervals of 28 days Rituximab IV infusion before FC infusion Cycle 1: 375mg/m² IV; do Cycles 2-6: 500mg/m² IV; d1 Fludarabine IV infusion over three days for six treatment cycles (25mg/m²/day IV; d1-d3) Cyclophosphamide IV infusion over three days for six treatment cycles (250mg/m²/day IV; d1-d3) C(ontrol): Fludarabine + Cyclophosphamide Fludarabine IV infusion over three days for six treatment cycles(25mg/m²/day IV; d1-d3) Cyclophosphamide IV infusion over three days for six treatment cycles (250mg/m²/day IV; d1-d3)
In-/exclusion criteria	Inclusion criteria: Patients with untreated, active B-cell CLL and good physical fitness (CIRS[1] score ≤6), Binet stage B and C requir-	Inclusion criteria: relapsed or refractory patients with B-cell CLL and ≤one previous chemotherapy, Binet stages A, B, C, ECOG[2]

[1] CIRS = Cumulative Illness Rating Scale

[2] ECOG = Eastern Cooperative Oncology Group

	ing treatment (certain criteria have to be fulfilled), age ≥18 years, expected survival >6 months, EC OG[2] performance status 0-1 Exclusion criteria: Binet stage A, prior chemotherapy and/or radiotherapy, clinically significant auto-immune cytopenia, Coombs-positive haemolytic anaemia as judged by the treating physician	Performance Status 0-1, age ≥18 years, expected survival >6 months, acceptable hematologic status, liver function, renal function and pulmonary function Exclusion criteria: prior treatment with Interferon, rituximab or other monoclonal antibody, prior allogeneic or autologous bone marrow transplant or peripheral stem cell transplant or patients who are considered to be candidates for those procedures as assessed by their treating physicians, severe grade 3 or 4 non-hematological toxicity or prolonged (>2 weeks) grade 3 or 4 cytopenia on prior fludarabine or nucleoside analogue regimen, history of fludarabine-induced or clinically significant autoimmune cytopenia
Follow-up	Median follow-up 25.4 months	Median follow-up 25.3 months
Outcomes	Primary: Progression-free survival (PFS) Secondary: Overall survival (OS), response rates, rates of treatment-related adverse effects	Primary: Progression-free survival (PFS) Secondary: Overall survival (OS), response rates
Key results	Primary: Median PFS at 25.4 months: I: 42.8 months vs. C: 32.5 months (p<0.001), HR[3]= 0.60 (95% CI[4] 0.48 – 0.76; p<0.001) PFS at 25.5 months: I: 76.6% vs. C: 62.3% (p<0.001) PFS at 26.4 months: I: 37.1 months vs. C: 30.8 months (p<0.001), HR=0.6 (95% CI 0.47 – 0.75; p<0.0001) Secondary: OS at 25.4 months: HR=0.72 (95% CI: 0.48, 1.09; p=0.13), at 25.5. months I: 91% vs. C: 88% (p=0.18); Mean OS at 26.4 months: I: 47.7 months vs. C: 48.2 (p=0.18) Response to treatment: Overall response rate I: 95% vs. C: 88% [p=0.001]; complete remission I: 44.5% vs. C: 22.9% [p<0.01]; partial remission I: 39.6% vs. C: 50.4% [p<0.01], progressive disease I: 3.3% vs. C: 8.1% [p<0.01]	Primary: Median PFS: I: 30.6 months vs. C: 20.6 months [p=0.0002], HR[3]= 0.65 (95% CI[4]: 0.51, 0.82) Secondary: Median OS: I: not reached vs. C: 51.9 months Response to treatment: Overall response rate I: 69.9% vs. C: 58.0% (p=0.0034); complete remission I: 24.3% vs. C: 13.0% [p=0.0007]; partial remission I: 45.7% vs. C: 44.9%; progressive disease I: 2.5% vs. C: 5.4%
Adverse effects	Grade 3/4 CTC[5] adverse events (I vs. C) Overall: 309 (77.5%) vs. 248 (62.6%) [p<0.0001]; Hematological toxicity 55.7% vs. 39.4% [p<0.0001] Neutropenia 33.7% vs. 21% [p<0.0001] Leukocytopenia 24% vs. 12.1% [p<0.0001] Thrombocytopenia 7.4% vs. 10.9% Anemia 5.4% vs. 6.8% Infection 18.8% vs. 14.9% Tumour Lysis Syndrome 0.2% vs. 0.5% Cytokine release syndrome 0.25% vs. 0.0% Treatment related mortality 2.0% vs. 1.5%	Grade 3/4 CTC[5] adverse events (I vs. C) Overall: 65pts (23.6%) vs. 60pts (21.7%) Infusion-related (d1-2 of first cycle): 6pts (2.2%) vs. 4pts (1.5%) Tumour Lysis Syndrome: 2pts (0.7%) vs. 3pts (1.1%) Neutropenia 42pts (15.2%) vs. 40pts (14.5%) Febrile Neutropenia: 15pts (5.4%) vs. 12pts (4.3%) Thrombopenia: 11pts (4%) vs. 9pts (3.3%) Autoimmune haemolytic anaemia: 5pts (1.8%) vs. 12pts (4.3%) Infections: 17pts (6.2%) vs. 19pts (6.9%)

[3] HR = Hazard Ratio

[4] CI = Confidence Interval

[5] CTC = Common Terminology Criteria

		Hepatitis B: 2pts (0.7%) vs. 0 pts (0%) Benign or malignant neoplasms: 7pts (2.5%) vs. 3pts (1.1%)
Commentary	7 pts. were excluded from all analyses due to missing informed consent. The ITT[6] population included 810 pts. (I: 403 vs. C: 407) As shown in multivariate analyses certain factors, including age, gender, Binet stage, CIRS score and renal function, were independently predicting PFS or OS.	

[6] ITT = Intention To Treat

median follow-up 25 months, no difference in overall survival between intervention and control group, grade 3/4 neutropenia and leukocytopenia occurred more often in the intervention arm compared to the control arm

Two phase III trials with a median follow-up of about 25 months have been conducted comparing FCR versus FC in patients both with previously untreated, active B-cell CLL and patients with relapsed/refractory B-cell CLL. Although both trials showed a significantly increased overall response rate, complete remission rate and progression-free survival in the FCR arm compared to the FC arm, there was no difference in overall survival between the intervention and control group. In terms of grade 3/4 adverse events, patients in the intervention group compared to the control group of CLL-8 were significantly more often affected by haematological toxicity, particularly neutropenia and leukocytopenia, even though no increased rates of infections were observed.

6.2 Efficacy and safety - further studies

FCR compared to other treatments, six year follow-up, historical comparison; no data on comparators provided

median age 57y, low and intermediate risk disease in two thirds of patients

Tam et al. [27] compared long-term results of a FCR regimen in 300 patients with previously untreated, active CLL in an open-label phase II trial with a historical comparison of 190 patients who had received other active treatments, such as fludarabine ± prednisone, fludarabine and cyclophosphamide or fludarabine and mitoxantrone. They concluded that the FCR regimen yielded the highest rates of complete remission, longest remission duration and most favourable survival. After a median follow-up of six years the overall survival was 77% and the failure[2]-free survival was 51%. Of note, data concerning the historical comparison group was not presented by the authors. The median age of patients in this study was 57y and only 14% of patients were aged 70 years or more. In addition, almost two thirds of patients were suffering from low and intermediate risk disease according to the Rai classification and only one third of patients were classified as having high risk disease. Both, complete remission rate and survival, were independently associated with age younger than 70 years, white cell count less than 150 x 10^9/L, absence of chromosome 17 abnormalities and beta-2-microglobulin less than twice the normal limit. In terms of adverse events, advanced Rai stage was associated with an increased risk of persistant cytopenia (>3 months) following completion of FCR therapy.

[2] Failure was defined as primary refractory disease, CLL progression (including development of Richter transformation), therapy-related myelodysplasia, or death.

Keating et al. [28] conducted a single-arm study of FCR in 224 patients with previously untreated, active CLL and concluded that FCR leads to a high rate of complete remission (70%). Nevertheless, the median age of patients enrolled was 58 years with only 13% of patients being 70 years or older. Furthermore, slightly more than two thirds of patients were suffering from low and intermediate risk disease according to the Rai classification and only one third of patients were classified as having high risk disease. 26% of patients did not complete six courses of therapy, mainly due to persistant cytopenia. Early discontinuation was significantly associated with advanced disease stage, older age, anaemia, impaired renal function and elevated beta-2-microglobulin levels.

sinlge-arm study FCR with 70% complete remission

median age 58y, low and intermediate risk disease in two thirds of patients, persistant cytopenia in 26% of patients

Wierda et al. [29] retrospectively compared three sequential groups of patients with recurrent or refractory CLL treated with fludarabine ±prednisone (n=251), FC (n=111) or FCR (n=143). Among those three groups, the longest estimated median survival was observed for patients who received FCR.

retrospective comparison of F±prednisone, FC, FCR

Tam et al. [30] assessed the FCR regimen for the treatment of patients with CLL or indolent NHL in an observational series. 77 patients with a median age of 59 years, of whom 34 were suffering from CLL - 12 of whom were suffering from previously untreated CLL - were treated with FCR. 18 of the 34 patient were classified low or intermediate risk disease according to the Rai classification. The FCR regimen yielded a high rate of complete remission and prolonged disease remissions. It is important to note, however, that this study assessed a small group of patients with heterogeneous characteristics in terms of age, disease, disease stage and previous treatments which complicates an extrapolation of results.

observational series of FCR, heterogeneous group of patients

Foon et al. [31] conducted a single-arm study of FCR in 48 patients with previously untreated CLL with a median age of 58 years, 83% of whom had low and intermediate risk disease according to the Rai classification. This study aimed at reducing the rate of grade 3/4 neutropenia by decreasing the dose of fludarabine and cyclophosphamide and increasing the dose of rituximab (FCR-Lite). Although grade 3/4 neutropenia could be reduced dramatically, an impact of FCR-Lite on overall survival has not been established yet which will be of utmost importance concerning the higher treatment costs, if rituximab is added at increased doses.

single-arm study of FCR-Lite, median age 58y, 83% low and intermediate risk disease

reduced grade 3/4 neutropenia, increased treatment costs

The study by Lamanna et al. [32], so far the only one which focused on patients with intermediate or high risk CLL, explored a sequential therapy with fludarabine, followed by cyclophosphamide and rituximab in 36 patients with a median age of 59 years with previously untreated CLL. They concluded that sequential treatment with FCR is superior to sequential treatment with FC in terms of improved quality of response. However, a sequential therapy of FCR has not yet been compared to the concomitant regimen of FCR in prospective randomised controlled trials.

sequential therapy with FCR in patients with intermediate and high risk CLL, median age 59y

Further studies assessed various regimens and combinations of rituximab, such as modified FCR regimens for CLL [33], new chemoimmunotherapy combinations for previously treated and untreated CLL [34-38], consolidation and maintenance immunotherapy with rituximab in patients with CLL [39], the addition of rituximab to fludarabine in patients with previously untreated CLL [40] and previously untreated ZAP-70 negative CLL [41].

further studies of rituximab in various diseases

7 Estimated costs

100mg vial EUR 308.75, 500mg vial EUR 1,492.75

In Austria rituximab is marketed by Roche Austria, Vienna. One package of 100mg rituximab (10mg/ml) concentrate for solution for infusion consisting of two single-use vials is € 616.15. In addition, one package of 500mg rituximab (10mg/ml) concentrate for solution for infusion containing one single-use vial is € 1,492.75 [42].

estimated total treatment costs EUR 15,734 in addition to chemotherapy

Assuming an average body surface area, based on height and weight, of 1.7 m^2 for both men and women, total treatment costs for the recommended rituximab regimen can be estimated. The first cycle of rituximab infusion would be € 2,109, followed by € 2,725 for cycle two to six (assuming that two packages containing two 100mg vials are used) which would add up to total treatment costs of € 15,734 in addition to chemotherapy.

8 Ongoing research

ongoing phase III studies of rituximab for first-line and maintenance therapy of CLL

There are a number of ongoing phase III trials of rituximab [21], such as

- NCT00769522: German CLL study group, Germany; CLL first-line therapy; primary outcome: progression-free survival; results expected 2018.
- NCT00645606: GOELAMS and FCGCLL/WM, France; CLL maintenance; primary outcome: progression-free survival; results expected 2012.

ongoing phase II studies of chemoimmunotherapies for first- and second-line treatment of CLL

There are several ongoing phase II trials assessing the effectiveness of rituximab in combination with various chemotherapy regimens for the treatment of previously untreated as well as relapsed/refractory CLL. In addition, rituximab is intensively investigated as maintenance therapy in CLL and other NHLs. Multiple second generation antibodies, such as ofatumumab, are under clinical development for the treatment of CLL as well. Furthermore, there are numerous phase II trials exploring the use of rituximab in different diseases, such as acute thrombotic thrombocytopenic purpura, multiple sclerosis, progressive sarcoidosis, and rheumatoid arthritis, besides others [43].

phase II study of fludarabine/rituximab and lenalidomide for first-line treatment of CLL

In Austria the Arbeitsgemeinschaft Medikamentöse Tumortherapie [44] is currently conducting a phase II trial (CLL-5 RevliRit) assessing fludarabine/rituximab in combination with lenalidomide, followed by rituximab/lenalidomide for the first-line treatment of CLL. Results are expected in 2011.

9 Commentary - English

CLL is the most common leukaemia in adults in industrialised countries and despite several treatment options still considered incurable except in a small group of patients eligible for allogeneic bone marrow transplantation. In addition to available treatment regimens, rituximab was approved by the EMEA for the first-line treatment of CLL patients in combination with chemotherapy. Moreover, a positive opinion concerning the second-line treatment of CLL patients in combination with chemotherapy has been issued by the EMEA in July 2009 [2].

EMEA approved rituximab for first-line treatment of CLL and issued positive opinion concerning second-line treatment of CLL

The CLL-8 trial demonstrated favourable outcomes in terms of PFS and complete remission rates for patients receiving FCR over patients receiving FC. In spite of encouraging results regarding improved overall survival in an interim analysis, the study failed to maintain this advantage during follow-up, but the authors [24] argue that this might have been due to subsequent lines of treatment as well as cross-over. The incidence of grade 3/4 adverse events, mainly haematological reactions occuring particularly during the first treatment cycles, was higher in the intervention than in the control group. Moreover, serious adverse events, the most common of which was febrile neutropenia, were observed in 46% of the FCR arm and in 41% in the FC arm. However, the percentage of deaths judged to be related to treatment was 2% in FCR and 1.5% in FC [2].

subsequent lines of treatment and cross-over were common in the CLL-8 trial

grade 3/4 haematological reactions occurred mainly during the first cycles

The choice of treatment regimen for CLL depends upon several factors, such as patient's age, disease stage, presence of cytogenetic lesions, concomitant diseases and - with second-line treatment – duration of response [11]. Chemotherapy mainly provides a treatment option for patients aged less than 70 years and in good clinical condition [15]. With Rituximab in combination therapy response rates increased by about 10%, PFS by 7 to 10 months, no effect on OS has been proven yet. As response rates and progression-free survival are believed to lead to a substantial gain in quality of life (while the effect from PFS on increased overall survival is under debate), FCR might be a treatment option for those patients but at the expense of increased toxicity. In contrast, as the majority of patients are diagnosed at the age of 70 or above, only a limited number of CLL patients might be suitable for this treatment. Of note, the trials presented in this report included mainly younger and fitter patients, making it difficult to judge possible positive and negative consequences for older individuals.

chemotherapy is an option mainly for patients younger than 70 years and in good clinical condition

increased therapy response rates and PFS, no effect on OS with rituximab

Overall, the chosen study populations as well as the comparator (FC only) in the two phase III studies seem to be appropriate for the intended target group but the study populations were younger and fitter than CLL patients in clinical practice [24]. Therefore, to assess the value of rituximab in older individuals with comorbidities who make up the majority of CLL patients, further trials both in comparison to and in combination with chlorambucil and other less aggressive regimens than FC are needed. Furthermore, rituximab is a potential add-on to any other CLL chemotherapy regimen other than FC because most of the FCR toxicity is caused by the FC part of the schedule.

need for further studies to assess value of rituximab in older patients with comorbidities

Because rituximab is an add-on to existing CLL treatment regimens and CLL is on the rise in Austria due to an ageing population, the financial impact of the licensure of rituximab for the treatment of CLL will be substantial.

substantial financial impact expected in Austria

10 Commentary – German

EMEA Zulassung von Rituximab für die first-line Therapie und positive Empfehlung bezüglich der second-line Therapie von CLL-PatientInnen

Die chronisch lymphatische Leukämie ist die häufigste Form der Leukämie Erwachsener in industrialisierten Ländern und wird trotz zahlreicher Behandlungsoptionen, mit Ausnahme einer kleinen Gruppe von PatientInnen, die für eine allogene Transplantation qualifiziert, als nicht heilbar erachtet. Zusätzlich zu bereits verfügbaren Behandlungsregimes wurde Rituximab von der EMEA für die first-line Therapie von CLL-PatientInnen in Kombination mit Chemotherapie zugelassen. Außerdem erfolgte eine positive Empfehlung bezüglich der second-line Therapie von CLL-PatientInnen mit Rituximab in Kombination mit Chemotherapie durch die EMEA im Juli 2009 [2].

Folgetherapien und cross-over waren in der CLL-8 Studie verbreitet

Die CLL-8 Studie zeigte einen Vorteil bezüglich progressionsfreien Überlebens von PatientInnen, die FCR erhielten, im Gegensatz zu jenen, die FC verabreicht bekamen. Eine in einer vorzeitig durchgeführten Datenanalyse erhobene verbesserte Überlebensrate im FCR Arm, konnte im weiteren Verlauf nicht bewiesen werden, wobei dies von den Autoren [24] auf nachfolgende Therapien sowie cross-over im FC Arm zurückgeführt wird. Die Inzidenz Grad 3/4 unerwünschter Nebenwirkungen, vor allem hämatologischer Natur, die vorwiegend in den ersten Therapiezyklen auftraten, war in der Interventionsgruppe höher als in der Kontrollpopulation. Schwerwiegende unerwünschte Nebenwirkungen, von denen die häufigste die febrile Neutropenie darstellte, traten bei 46% der PatientInnen im FCR Arm und bei 41% der PatientInnen im FC Arm auf. Der prozentuelle Anteil der Todesfälle, welche mit der Therapie in Verbindung gebracht wurden, betrug zwei Prozent im FCR Arm und 1.5% im FC Arm [2].

Grad 3/4 unerwünschter Nebenwirkungen traten vorwiegend in den ersten Therapiezyklen auf

Chemotherapie stellt vorwiegend eine Behandlungsoption von PatientInnen unter 70 Jahren in gutem Allgemeinzustand dar

Die Wahl der jeweiligen Behandlungsmethode für CLL PatientInnen hängt von mehreren Faktoren, wie dem Alter der Patientin/des Patienten, dem Stadium der Erkrankungen, dem Vorhandensein zytogenetischer Läsionen, der Komorbidität und – im Falle der second-line Therapie –der Dauer der Remission, ab [11]. Chemotherapie stellt hauptsächlich eine Behandlungsoption von PatientInnen unter 70 Jahren dar, die sich in einem guten Allgemeinzustand befinden [15]. Mit Rituximab als Kombinationstherapie erhöhte sich die Remissionsrate um circa 10%, und progressionsfreies Überleben verlängerte sich um sieben bis zehn Monate, jedoch konnte eine Verlängerung des Gesamtüberlebens nicht bewiesen werden. Da man davon ausgeht, dass Remission und progressionsfreies Überleben zu einer beträchtlichen Verbesserung der Lebensqualität führen (wobei der Effekt des verlängerten progressionsfreien Überlebens auf das Gesamtüberleben derzeit noch diskutiert wird), könnte FCR einen wertvollen Beitrag zu bestehenden Behandlungsmethoden liefern, jedoch mit dem Nachteil einer erhöhten Toxizität. Auf der anderen Seite ist der Großteil der PatientInnen bei Diagnosestellung ≥ 70 Jahre alt, wodurch ohnehin nur ein kleiner Anteil an CLL PatientInnen für diese Therapie in Frage kommen würde. Von Interesse ist, dass die hier präsentierten Studien hauptsächlich jüngere PatientInnen in gutem Allgemeinzustand inkludierten, sodass es schwierig ist, daraus Rückschlüsse auf ältere Personen zu ziehen.

erhöhte Remissionsraten, verlängertes progressionsfreies Überleben, jedoch keine Verlängerung des Gesamtüberlebens mit Rituximab

Zusammenfassend scheinen die gewählten Studienpopulationen sowie die Kontrolle (FC) der beiden Phase III Studien zwar angemessen für die Zielpopulation gewesen zu sein, die StudienteilnehmerInnen waren jedoch jünger und befanden sich in besserem Allgemeinzustand als CLL PatientInnen in der klinischen Praxis [24]. Um den Nutzen von Rituximab für ältere Personen mit Begleiterkrankungen, welche den überwiegenden Teil der CLL PatientInnen ausmachen, bewerten zu können, wären weitere Studien im Vergleich zu beziehungsweise in Kombination mit Chlorambucil und anderen weniger aggressiven Regimes als FC wünschenswert.

weitere Studien zur Nutzenbewertung von Rituximab für ältere PatientInnen mit Begleiterkrankungen wünschenswert

Rituximab stellt eine potentielle Erweiterung jeder CLL Chemotherapie neben FC dar, umsomehr als der größte Teil der FCR Toxizität durch den FC Teil des Regimes bedingt ist.

Da der Einsatz von Rituximab in der Therapie der CLL eine additive Erweiterung existierender Behandlungskonzepte darstellt und die CLL in Österreich im Zunehmen begriffen ist, müssen die finanziellen Auswirkungen der Zulassung von Rituximab zur Behandlung der CLL als gravierend eingeschätzt werden.

gravierende finanzielle Auswirkungen in Österreich erwartet

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