Horizon Scanning in Oncology

Rituximab (Rituxan®/MabThera®) for the first- and second-line treatment of chronic lymphocytic leukaemia
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Vienna, October 2009
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Publisher:
Ludwig Boltzmann Gesellschaft GmbH
Operngasse 6/5, Stock, A-1010 Vienna
http://www.lbg.ac.at/gesellschaft/impressum.php

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DSD: Horizon Scanning in Oncology Nr. 004
ISSN online 2076-5940
http://eprints.hta.lbg.ac.at/view/types/
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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 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].

The recommended treatment regimen consists of six treatment cycles of rituximab in combination with fludarabine and cyclophosphamide at intervals of 28 days (= 1 cycle). Rituximab is administered only once at the beginning of every cycle with an initial starting dose of 375mg/m² body surface area (BSA) intravenously (IV) (Cycle 1), followed by 500mg/m² IV (Cycle 2-6) [2].

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 10⁹/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].

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].

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

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

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

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

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].

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].

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 in the peripheral blood for ≥3 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].

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].

The prognosis of CLL depends upon several factors and 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].

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].

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].

In Austria the overall incidence of all forms of leukaemia (C91-C95) 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.

### 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]

- Observation/watchful waiting

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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
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

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.

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

observation, chemotherapy, chemoimmunotherapy, involved-field radiation therapy, radioimmunotherapy, anti-CD52 monoclonal antibody, bone marrow and peripheral stem cell transplantation
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].

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.

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, vincristine, prednisolone (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.

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].

6 Evidence

To date, no randomised controlled trials concerning the first- and second-line treatment of CLL with rituximab, fludarabine and cyclophosphamide (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

FDA approval for non-Hodgkin lymphomas and rheumatoid arthritis

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

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

FDA supplemental Biologics License Applications for first- and second-line treatment of CLL
section 6.2) have assessed the combination of FCR in the first- and second-line treatment of CLL.

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

<table>
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<tbody>
<tr>
<td>EUDRACT-2004-004938-14</td>
<td>ISRCTN02757147 NCT00381918</td>
<td>NCT00090051</td>
</tr>
<tr>
<td>Sponsor</td>
<td>Hoffmann-La Roche Ltd, Basel, Switzerland</td>
<td>Biogen Idec. Collaborators: Hoffmann-La Roche, Genentech</td>
</tr>
<tr>
<td>Country</td>
<td>Multicentre – International (190 study sites across 11 countries)</td>
<td>Multicentre – International (88 study sites across 17 countries)</td>
</tr>
<tr>
<td>Design</td>
<td>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)</td>
<td>Randomised, open-label , active control</td>
</tr>
<tr>
<td>Participants characteristics</td>
<td>n=817 patients (pts) (I: 408 vs. C: 409); median age I: 61y (30-80y), C: 61y (36-81y);</td>
<td>n=552 patients (pts) (I:276 vs. C:276); median age I: 63y (35-83y), C: 62y (35-81y);</td>
</tr>
<tr>
<td>Treatments</td>
<td>(Intervention): Rituximab + Fludarabine + Cyclophosphamide for a total of six treatment cycles at intervals of 28 days</td>
<td>(Intervention): Rituximab + Fludarabine + Cyclophosphamide for a total of six treatment cycles at intervals of 28 days</td>
</tr>
<tr>
<td></td>
<td>Rituximab IV infusion before FC infusion Cycle 1: 375mg/m² IV; do</td>
<td>Rituximab IV infusion before FC infusion Cycle 1: 375mg/m² IV; do</td>
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<tr>
<td></td>
<td>Cycle 2-6: 500mg/m² IV; d1</td>
<td>Cycles 2-6: 500mg/m² IV; d1</td>
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<td></td>
<td>Fludarabine IV infusion over three days for six treatment cycles (25mg/m²/day IV; d1-d3)</td>
<td>Fludarabine IV infusion over three days for six treatment cycles (25mg/m²/day IV; d1-d3)</td>
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<td>Cyclophosphamide IV infusion over three days for six treatment cycles (250mg/m²/day IV; d1-d3)</td>
<td>Cyclophosphamide IV infusion over three days for six treatment cycles (250mg/m²/day IV; d1-d3)</td>
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<tr>
<td></td>
<td>(Control): Fludarabine + Cyclophosphamide</td>
<td>(Control): Fludarabine + Cyclophosphamide</td>
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<tr>
<td></td>
<td>Fludarabine IV infusion over three days for six treatment cycles (25mg/m²/day IV; d1-d3)</td>
<td>Fludarabine IV infusion over three days for six treatment cycles (25mg/m²/day IV; d1-d3)</td>
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<tr>
<td></td>
<td>Cyclophosphamide IV infusion over three days for six treatment cycles (250mg/m²/day IV; d1-d3)</td>
<td>Cyclophosphamide IV infusion over three days for six treatment cycles (250mg/m²/day IV; d1-d3)</td>
</tr>
<tr>
<td>In-/exclusion criteria</td>
<td>Inclusion criteria: Patients with untreated, active B-cell CLL and good physical fitness (CIRS1 score ≤ 6), Binet stage B and C</td>
<td>Inclusion criteria: relapsed or refractory patients with B-cell CLL and one previous chemotherapy, Binet stages A, B, C, ECOG2</td>
</tr>
</tbody>
</table>

1 CIRS = Cumulative Illness Rating Scale
2 ECOG = Eastern Cooperative Oncology Group
ing treatment (certain criteria have to be fulfilled), age \( \geq \) 18 years, expected survival > 6 months, ECOG 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 \( \geq \) 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

**Key results**

- **Primary:**
  - Median PFS at 25.4 months: I: 42.8 months vs. C: 32.5 months (p<0.001), HR=0.60 (95% CI: 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<0.001); partial remission I: 39.6% vs. C: 50.4% (p<0.01), progressive disease I: 3.3% vs. C: 8.1% (p<0.01)

**Adverse effects**

- Grade 3/4 CTC5 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 0.2% vs. 0.0%
  - Treatment related mortality 2.0% vs. 1.5%

- Grade 3/4 CTC 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: 19pts (5.4%) vs. 12pts (4.3%)
  - Thrombocytopenia: 11pts (4%) vs. 9pts (3.3%)
  - Autoimmune haemolytic anaemia: 5pts (1.8%) vs. 12pts (4.3%)
  - Infections: 17pts (6.2%) vs. 19pts (6.9%)

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3 HR = Hazard Ratio
4 CI = Confidence Interval
5 CTC = Common Terminology Criteria
Horizon Scanning in Oncology

| Commentary | Hepatitis B: 2 pts (0.7%) vs. 0 pts (0%)  
| Benign or malignant neoplasms: 7 pts (2.5%) vs. 3 pts (1.1%)  
 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

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

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 failure²-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.

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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 persistent cytopenia. Early discontinuation was significantly associated with advanced disease stage, older age, anaemia, impaired renal function and elevated beta-2-microglobulin levels.

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.

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 patients 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.

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.

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.

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].
7 Estimated costs

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].

Assuming an average body surface area, based on height and weight, of 1.7 m² 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

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.

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].

In Austria the Arbeitsgemeinschaft Medikamentöse Tumortherapie [44] is currently conducting a phase II trial (CLL-5 RevliRit) assessing fludarabine/rituximab and 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].

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 occurring 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].

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.

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.

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.


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 bessarem 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.

Rituximab stellt eine potentielle Erweiterung jeder CLL Chemotherapie neben FC dar, umso mehr 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.

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

gravierende finanzielle Auswirkungen in Österreich erwartet
References


