

# Horizon Scanning in Oncology

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remission in patients with  
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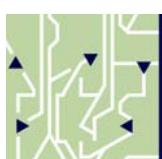
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# 1 Drug description

## Generic/Brand name:

Ibritumomab tiuxetan/ Zevalin®

## Developer/Company:

Manufacturer of the biological active substance is Biogen IDEC, USA, the manufacturer responsible for batch release is Bayer Schering Pharma AG [1].

## Description:

Ibritumomab tiuxetan (Zevalin®) is a radioimmunotherapy drug which is administered in combination with rituximab. It is the immunoconjugate of ibritumomab, a monoclonal antibody, and tiuxetan, a chelator for the radionucleotide yttrium-90. Zevalin® binds specifically to the antigen CD20 of B-lymphocytes which is expressed on pre-B and mature B-lymphocytes and on malignant B-lymphocytes. Before ibritumomab tiuxetan can be used, it has to be radiolabelled by attaching the radioactive element yttrium-90. The monoclonal antibody targets the CD20 antigen and the β-emission from yttrium-90 with a mean path length of 5mm results in the induction of cellular damage of both targeted and neighbouring cells. In order to deliver the radiation more precisely to the lymphomas, rituximab (in a reduced dose compared to the approved monotherapy) should be used as pre-treatment to eliminate circulating CD20 positive B-lymphocytes [1, 2] and to saturate any unspecific bindings.

If ibritumomab tiuxetan is administered as consolidation therapy after remission induction, patients with  $\geq 150,000$  platelets per  $\text{mm}^3$  should receive 15MBq/kg (megabecquerel per kilogram) body weight up to a maximum of 1200MBq. Patients with a lower platelet count should not receive ibritumomab tiuxetan at all [1]. This means that marrow infiltration by the lymphoma should not exceed 25%. Rituximab has to be given twice, one week before (day 1) and immediately prior (day 7, 8 or 9) to Zevalin® administration which is given only once as slow intravenous infusion over ten minutes [1].

ibritumomab tiuxetan,a  
radioimmunotherapy  
drug, targets the CD20  
antigen of B-  
lymphocytes

as consolidation therapy  
for the treatment of  
follicular lymphomas

# 2 Indication

Ibritumomab tiuxetan is indicated as consolidation therapy after first remission induction in patients with follicular lymphoma.

### 3 Burden of disease

**FL are non-Hodgkin's lymphomas, a heterogeneous group of lymphoproliferative disorders the majority is indolent**

**symptoms include enlarged lymph nodes, weight loss, fever**

**an estimated 220 cases annually in Austria**

**treatment decisions influenced by cell of origin, immunophenotype and stage of disease**

**prognosis depends on age, disease stage, number of nodal areas affected, ...**

**10-year survival rate ranges from 40%-85%**

Follicular lymphomas (FL) are the 2<sup>nd</sup> most common entity among B-cell non-Hodgkin's lymphomas (NHL) which are a heterogeneous group of lymphoproliferative disorders. Within NHL, indolent and aggressive lymphomas are differentiated, a classification based on differences in prognosis. Depending on the number of centroblasts the Revised European-American Classification of Lymphoid Neoplasms (REAL) and WHO guidelines classify FLs into three grades. The majority of FLs are indolent lymphomas consistent with grade 1 or 2, whereas aggressive forms are of grade 3a and 3b [3, 4].

Symptoms include enlarged lymph nodes, either isolated or disseminated, and the so called B-symptoms which include weight loss, fever or night sweats. Besides lymph nodes, the spleen, the bone marrow or the skin are most commonly affected. Risk factors are older age, male gender, white ethnicity, inherited immune disorders (e.g. hypogammaglobulinemia), autoimmune diseases, such as Sjögren-syndrome or rheumatoid arthritis, and infections with HIV/AIDS, Epstein-Barr virus or Helicobacter pylori [5].

In 2006, 991 new NHL cases were diagnosed and 541 NHL related deaths occurred in Austria [6]. The International Lymphoma Classification Project which evaluated 1,402 lymphoma cases, comprising more than 90% of all NHL cases in the United States, identified 22% as being follicular lymphomas [4]. Applying the same percentage to the overall NHL incidence in Austria, indicates 220 follicular lymphoma cases annually. The NHL incidence has constantly risen over the last decades, particularly in older people in their 60s or 70s, mainly due to a reduction of mortality from other causes [4]. Median age at diagnosis is about 65 years [7], a fact related to the high probability of co-morbidities [4].

To verify diagnosis a biopsy should be performed by reason that therapeutic decisions are influenced by the cell of origin, immunophenotype and other genetic attributes [4]. Another factor relevant to the choice of treatment is whether the disease is localized or advanced, corresponding to Ann Arbor stage III or IV. This classification system comprises four stages (I-IV) based on the number and regions of lymph nodes affected, involvement of extra lymphatic organs/sites and whether these lesions are on the same side or on both sides of the diaphragm [3]. Within these four groups, two subcategories (A and B) can be distinguished based on the presence or absence of B-symptoms.

Risk factors influencing the prognosis are summarized in the Follicular Lymphoma International Prognostic Index (FLIPI) and include age, serum lactate dehydrogenase level, disease stage (Ann Arbor), haemoglobin level and number of nodal areas affected ( $\leq 4$  vs  $> 4$ ). Additional to these factors, age, performance status, tumour size and the presence of bulky disease are known to impact on the prognosis [3]. Depending on the number of risk factors present, the 10-year survival rate ranges from 40% to 85% [3]. Even though patients with FL most often present with disseminated disease [3], median survival ranges from 8 to 15 years leading to the annotation of being indolent. Relapse to more aggressive forms is possible, resulting in a diminished median survival of 1 to 2 years after transformation and a 10-year survival of only 10% to 20% of patients [3].

## 4 Current treatment

Choice of treatment depends on disease stage, age, co-morbidities and future treatment possibilities, such as eligibility for high-dose therapy (e.g. autologous stem cell rescue), and is therefore highly individualized.

Observation is an option as long as there are none of the following symptoms present: ≥3 nodal sites involved, extra-, nodal tumor mass ≥7 cm in diameter, B symptoms, pleural effusions or peritoneal ascites, cytopenias or leukemia.

If treatment is indicated, options for both first- and second-line therapy are:

- ❖ Locoregional radiation therapy
- ❖ Chemotherapy (cyclophosphamide, vincristine, doxorubicin, fludarabine, mitoxantrone, chlorambucil, bendamustine in various combinations and often including further chemotherapeutic agents like etoposide or platinum-derivatives)
- ❖ Immunotherapy (rituximab)
- ❖ Chemo-immunotherapy
- ❖ Radioimmunotherapy (tositumomab (Bexxar®) only available in the USA)
- ❖ High dose therapy with autologous or allogeneic stem cell rescue (only as second-line treatment) [4].

**several treatment options for first- and second-line therapy...**

**observation,**  
**radiation therapy,**  
**chemotherapy,**  
**immunotherapy,**  
**chemo-immunotherapy,**  
**radioimmunotherapy,**  
**stem cell rescue**

The National Cancer Comprehensive Network (NCCN) has given a category 1<sup>a</sup> recommendation for cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) + rituximab (R-CHOP), for cyclophosphamide, vincristine, prednisone (CVP) + rituximab and for chemotherapy followed by radioimmunotherapy as first-line therapy. Category 1 treatment options for second-line therapy include fludarabine, cyclophosphamide, mitoxantrone + rituximab (FCMR) and radioimmunotherapy.

In addition to these indications, rituximab can also be used as first-line maintenance therapy but preferably within clinical trials. Furthermore, it is recommended as first-line therapy for elderly or infirm patients who are not eligible for chemotherapy and as second-line maintenance therapy [4].

## 5 Current regulatory status

The EMEA granted marketing authorization for ibritumomab tiuxetan

- ❖ for the treatment of adult patients with rituximab relapsed or refractory CD20+ follicular B-cell NHL in January 2004.

<sup>a</sup> NCCN category 1 = The recommendation is based on high-level evidence, and there is uniform NCCN consensus.

**approved by the EMEA  
and the FDA after  
remission induction in  
previously untreated  
patients with FL**

- ❖ for the consolidation therapy after remission induction in previously untreated patients with follicular lymphoma in April 2008 [1]. The benefit of Zevalin® following rituximab in combination with chemotherapy has not been established

Indications approved by the U.S. Food and Drug Administration (FDA) are

- ❖ relapsed or refractory, low-grade or follicular B-cell NHL (February 2002).
- ❖ previously untreated patients with follicular NHL who achieve a partial or complete response to first-line chemotherapy (March 2009) [2].

## 6 Evidence

**one phase III trial, three  
phase II trials were  
identified**

Overall, four studies - one phase III trial and three phase II trials - were identified. The former, which compared consolidation therapy of ibritumomab tiuxetan to no further treatment after initial response to first-line chemotherapy, showed marked improvements for the intervention group as median progression-free survival (PFS) was prolonged by 23 months. This held true, even if patients were stratified according to the extent of their initial response. No differences - either for overall survival or for quality of life - were found between the intervention and the control group.

The three phase II studies (without control groups) yielded similar results. In patients pre-treated with chemotherapy, complete response rates increased, if ibritumomab tiuxetan was given after initial chemotherapy.

Overall, adverse events were very common and consisted primarily of transient myelosuppression. However, only a minority of patients (about 7%) required hospitalization for the treatment of these toxic effects.

### 6.1 Efficacy and safety - Phase III studies

<b>Reference</b>	published [8, 9] NCT00185393
<b>Sponsor</b>	Bayer Schering Pharma AG, Berlin, Germany
<b>Country</b>	International, 77 study centres in 12 European countries (United Kingdom, Belgium, France, Italy, Netherlands, Norway, Denmark, Sweden, Spain, Portugal, Germany, Switzerland) and Canada
<b>Design</b>	randomized , open-label, placebo-controlled
<b>Participants characteristics</b>	414 patients (I=208 vs C=206) median age I 55 years (range 29 – 78 years) vs C 53 years (range 27 – 74 years)
<b>Treatments</b>	I(ntervention):  250 mg/m <sup>2</sup> body surface area rituximab IV at day -7 and at day 0, followed by

	<p><math>90\text{Y}</math>-ibritumomab tiuxetan 14.8 MBq<sup>2</sup>/kg (maximal total dose 1.148 MBq) on day 0</p> <p><u>C</u>(ontrol): no treatment</p>
<b>In-/exclusion criteria</b>	<p><u>I</u>nclusion criteria: histological confirmed CD20+, grade 1 or 2 follicular lymphoma (REAL /WHO classification), stage III or IV disease at diagnosis, WHO performance status of 0 to 2, CR/CRu<sup>3</sup> or PR<sup>4</sup> (International Workshop criteria) after first-line chemotherapy (chlorambucil, CVP, CHOP, CHOP-like, fludarabine or rituximab combinations) administered 6 to 12 weeks before start of the study treatment</p> <p><u>E</u>xclusion criteria: prior radiation therapy or myeloablative therapy, symptomatic CNS lymphoma</p>
<b>Follow-up</b>	median observation period of 3.5 years
<b>Outcomes</b>	<p><u>P</u>rimary: overall PFS<sup>5</sup>, PFS stratified by response to first-line induction therapy (i.e. PR, CR/CRu)</p> <p><u>S</u>econdary: PFS based on type of first-line induction therapy, PFS according to FLIPI<sup>6</sup> scores, improvement in CR rate, overall survival (OS), safety, health-related quality of life</p>
<b>Key results</b>	<p><b>Primary:</b> median PFS overall: I 36.5 months vs C 13.3 months; HR = 0.465 (CI: 0.357, 0.605; p &lt; 0.0001)</p> <p>median PFS according to response to first-line therapy:            PR after first-line induction treatment: median PFS time I 29.3 months vs C 6.2 months, HR = 0.304 (CI: 0.213, 0.434; p &lt; 0.0001)            CR/CRu after first-line induction treatment: median PFS time I 53.9 months vs C 29.5 months; HR = 0.613 (CI: 0.410, 0.914; p = 0.0154)</p> <p><b>Secondary:</b>            - median PFS according to type of first-line therapy:            Chlorambucil I NR<sup>7</sup> vs C 11.9 months, HR<sup>8</sup> = 0.344 (CI<sup>9</sup>: 0.150, 0.793; p = 0.0088)            CVP/COP: I 28.5 months vs C 7.9 months, HR = 0.383 (CI: 0.235, 0.625; p = 0.0001)            CHOP: I 35.9 months vs C 12.5 months, HR = 0.391 (CI: 0.246, 0.622; p &lt; 0.0001)            CHOP-like I NR vs C 29.2 months, HR = 0.474 (CI: 0.219, 1.029; p = 0.0533)            Fludarabine combination I 41.4 months vs C 24.3 months; HR = 0.884 (CI: 0.283, 2.769; p = 0.8332)            Rituximab combination I NR vs C NR, HR = 0.722 (CI: 0.304, 1.714; p = 0.4583)              - median PFS according to FLIPI risk score:            low I NR vs C 24.1 months, HR 0.599 (CI: 0.357, 1.006; p = 0.0502)            intermediate I 53.9 months vs C 11.3 months, HR = 0.227 (CI: 0.134, 0.385; p &lt; 0.0001)            high I 23.8 months vs C 6.5 months, HR = 0.587 (CI: 0.322, 1.070; p = 0.0789)              - pts converting from PR after induction therapy to CR/CRu I 77% vs C 17.5%</p>

<sup>2</sup> MBq = Mega-Becquerel

<sup>3</sup> CR = complete response, CRu = unconfirmed complete response

<sup>4</sup> PR = partial response

<sup>5</sup> PFS = progression-free survival

<sup>6</sup> FLIPI = Follicular Lymphoma International Prognostic Index

<sup>7</sup> NR = not reached

<sup>8</sup> HR = Hazard Ratio

<sup>9</sup> CI = 95% Confidence Interval

	(p<0.001)  - no difference in OS between study arms  - health-related quality of life: mean EQ-5D <sup>10</sup> scores (baseline/final visit): I 0.83/0.84 vs C 0.84/0.83 mean VAS <sup>11</sup> -score (baseline/final visit): I 77.52/77.64 vs C 76.57/78.60
<b>Adverse effects</b>	<b>grade 3:</b> lymphopenia I 60.3% vs C 10.8%; neutropenia: I 40.2% vs C 2.0%, thrombocytopenia I 58.8% vs C 0%, anemia I 2.9% vs C 0% Infections I 6.9% vs C 2.4%, pyrexia I 2.5% vs C 0%  <b>grade 4:</b> lymphopenia I 0% vs C 0%, neutropenia I 26.5% vs C 0.5%, thrombocytopenia I 2.0% vs C 0%, anemia I 0.5% vs C 0% Infections I 1.0% vs C 0%, pyrexia I 0.5% vs C 0%  <b>deaths:</b> I 6 pts (1 neutropenic sepsis after subsequent chemotherapy, 1, pancreatic carcinoma, 1 acute myeloblastic leukemia (AML), 3 pts due to progressive disease) vs C 5 pts (1 sepsis, 4 due to progressive disease)  7.4% of the intervention group required hospitalization because of infections 1 AML case 2 years after ibritumomab tiuxetan therapy
<b>Commentary</b>	consolidation therapy with ibritumomab tiuxetan in patients achieving an initial response to first-line induction treatment is well tolerated with no unexpected toxicities and significantly prolongs PFS by 2 years compared with no further treatment.

<sup>10</sup> EQ-5D = EuroQoL-5D<sup>11</sup> VAS = Visual Analogue Scale

a phase III study assessed ibritumomab tiuxetan after first remission with various chemotherapy regimens in 414 patients

median PFS in comparison to no additional treatment was improved by about 2 years

no improvements in overall survival or health-related quality of life

This randomized controlled trial assessed ibritumomab tiuxetan as consolidation therapy in patients after first remission with various chemotherapy regimens, including rituximab based regimens. The study population was slightly younger than patients usually diagnosed with FL. Baseline characteristics were well balanced within the two groups and consisted of patients with FL at Ann Arbor stage III and IV and mainly at low (I 37% vs C 43%) or intermediate (I 39% vs C 37%) FLIPI risk.

Substantial improvements in median PFS were demonstrated for patients treated with ibritumomab tiuxetan in comparison to no additional treatment (HR=0.47), an effect independent of response to initial treatment. Adverse effects, including serious events such as myelosuppression, were more common in the intervention group (in up to 60% of patients) than in the control group, requiring hospitalization in 7% of patients. Six patients died in the intervention group and five in the control group.

Based on the relatively short median follow-up of 3.5 years, improvements in overall survival have not been established yet. No differences were observed in outcomes associated with health-related quality of life, including pain scores. Moreover, only 14% of patients had received rituximab containing regimens as first-line therapy which might not reflect standard practice of FL treatment [10]. For these patients, treatment with ibritumomab tiuxetan in comparison to no treatment did not lead to favourable results in terms of PFS.

## 6.2 Efficacy and safety - further studies

A phase II study [11] evaluated ibritumomab tiuxetan and extended rituximab after short-course CHOP-R therapy in 60 previously untreated FL patients. The study population comprised mainly patients < 60 years (65%) with higher stage FL (> 90% stage III or IV) or bulky FL and at intermediate and high FLIPI risk (75%). In an intention-to-treat analysis, the CR rate determined by computer tomography was 40% after CHOP-R and increased to 82% with radioimmunotherapy and extended rituximab. During a mean estimated follow-up of 19 months, 10 patients progressed of whom 8 had previously achieved CR, one PR and one stable disease. Adverse events associated with radioimmunotherapy were mostly myelosuppression, leading to neutropenia in 51% of patients and to thrombocytopenia in 44% of patients. However, only one patient required admission to hospital for the treatment of neutropenic fever.

Zinzani *et al.*[12] assessed fludarabine and mitoxantrone followed by ibritumomab tiuxetan in previously untreated FL patients. They included 61 patients with stage III or IV, indolent FL. Consolidation treatment with ibritumomab tiuxetan was administered only, if at least PR was achieved after six cycles of chemotherapy with fludarabine and mitoxantrone. Adding ibritumomab tiuxetan to the chemotherapy regimen resulted in a CR in 12 out of 14 patients who had initially achieved PR only. During a median follow-up time of 30 months, 10 patients progressed, leading to an estimated 3-year PFS of 76% and an estimated 3-year overall survival of 100%. Despite relatively frequent grade 3 or 4 haematological toxic effects (neutropenia in 30, thrombocytopenia in 36 and anaemia in 13 out of 57 patients), treatment was never discontinued and only two patients required hospitalization due to febrile neutropenia.

In a phase II trial conducted by Hainsworth *et al*[13], ibritumomab tiuxetan after short-course chemoimmunotherapy with rituximab either in combination with CHOP or CVP was evaluated in 41 patients. The study population was similar to the studies mentioned above, except that the majority of patients (83%) had either low or intermediate FLIPI scores. CR/CRu increased from 30% after chemoimmunotherapy to 72% after the administration of Zevalin® and only one patient progressed. At the end of the follow-up, median PFS was not yet reached but estimated 3- and 5-year PFS rates were 75% and 64%, respectively. Reported side-effects were consistent with the other studies.

three phase II trials showed increased complete response rates after administration of ibritumomab tiuxetan

adverse events, mostly myelosuppression, were common

## 7 Estimated costs

In Austria, one kit of radiopharmaceutical preparation for Zevalin® infusion, containing one vial of 3.2 mg (1,6mg/ml), is € 10,733.- [14]. As treatment is delivered only once, these costs display the overall costs for ibritumomab therapy but have to be added to expenses for induction therapies, as well as the concomitant rituximab therapy.

costs: €10,733 in addition to induction therapies and rituximab

## 8 Ongoing research

**ongoing trials assess  
Zevalin® for other  
indications/other NHL  
entities**

Two phase III studies were identified on clinical.trials.gov [15]:

[NCT00491491](#): adding Zevalin® to the conditioning regimen given prior to carmustine, etoposide, cytarabine and melphalan (BEAM) high-dose chemotherapy and autologous stem cell transplantation in patients with aggressive lymphoma.

[NCT00463463](#) which is not yet recruiting eligible patients. The aim is to compare Zevalin® and BEAM high-dose chemotherapy versus BEAM alone to determine the potential of Zevalin® radioimmunotherapy in improving the outcome of autologous stem-cell transplantation.

Additionally, several phase I and phase II studies were found. Research topics include ibritumomab tiuxetan for the treatment of FL in combination with various chemotherapy regimens, with chemotherapy prior to autologous stem cell transplantation and ibritumomab tiuxetan as first-line therapy for patients with FL or for FL of grade 1 or 2. Furthermore, the use of Zevalin® is under evaluation in other NHL entities such as mantle cell NHL [16] or diffuse large B-cell lymphomas [17].

## 9 Commentary

**despite EMEA market  
authorization in 2008,  
widespread use is  
hampered in Austria**

**improvements in  
progression-free  
survival by about 2  
years**

**most common side-  
effects were transient  
hematologic toxicities**

Based on one phase III study, the EMEA granted market authorization for Zevalin® for consolidation therapy after remission induction in previously untreated patients with FL in April 2008. Despite the long period of time since market approval, reasons hampering the widespread use of Zevalin® might include uncertainty about delayed adverse effects, such as secondary malignancies or bone marrow damage, the necessary treatment shift from haematologists to nuclear medicine physicians [10] and the limited availability of specialized centres with the required technical conditions for treatment delivery in Austria.

One phase III study showed substantial improvements in PFS of approximately 2 years in patients receiving Zevalin® after first remission in comparison to no further treatment. Additionally, 77% of patients who had initially achieved PR after induction chemotherapy converted to CR/CRu. These findings were consistent even if patients were stratified by response to first-line induction therapy and, in the majority, regardless of the type of induction chemotherapy. In all studies presented in this report, the most common side effects were transient hematologic toxicities, which occurred frequently but were manageable with platelet infusions and red blood cell transfusions. However, the risk of potential long-term adverse effects (e.g. myelodysplastic syndromes or acute myeloid leukaemia) associated with the exposure to ionising radiation, has not yet been clarified [18]. Additionally, no differences between the two groups could have been shown in terms of overall survival, probably due to the relative short observation period. Health-related quality of life and pain scores were also not improved by Zevalin®.

Even though the study was not designed to detect differences based on initial chemotherapy regimens, the authors present results for the individual subgroups. For the considerably small group of patients pre-treated with rituximab (overall only 59 patients), median PFS was not superior for the intervention compared to the control group. Since current FL therapy regimens most frequently incorporate rituximab, the additional benefit of ibritumomab tiuxetan for patients pre-treated with rituximab remains unclear [10]. On the one hand, the impressive extension of overall PFS might also hold true for patients pre-treated with rituximab. On the other hand, adding ibritumomab tiuxetan increases treatment costs, probably even at the expense of an augmented risk of adverse events and without any additional benefit.

Additional to data legitimising the use of this combination, the comparison of ibritumomab tiuxetan with rituximab is of further interest. As maintenance therapy with rituximab has also shown impressive results [19], clinical benefits either for rituximab based maintenance therapy or for ibritumomab tiuxetan consolidation therapy might be established [8, 10]. Furthermore, the importance of Zevalin® might increase, once results of ongoing trials evaluating it as first-line therapy and in other B-NHL subtypes and clinical settings become available. Zevalin® might also play a role in patients unsuitable for extended conventional chemotherapies.

**current therapy regimens most often incorporate rituximab**

**benefit of ibritumomab tiuxetan for patients pre-treated with rituximab remains unclear**

## 10 Commentary – German

Basierend auf einer Phase III Studie erteilte die EMEA im April 2008 die europäische Marktzulassung für Zevalin® als Konsolidierungstherapie bei zuvor unbehandelten PatientInnen mit folliculärem Lymphom (FL), die auf eine Induktionstherapie angesprochen hatten. Obwohl Ibritumomab Tiuxetan daher schon längere Zeit zugelassen ist, könnten Faktoren wie Unsicherheit bezüglich der Langzeitfolgen (sekundäre Malignome, Knochenmarkschäden) oder der notwendige Zuständigkeitswechsel von OnkologInnen zu NuklearmedizinerInnen, ebenso wie die begrenzte Anzahl an Zentren mit entsprechender technischer Einrichtung, die breite Anwendung in der klinischen Praxis in Österreich limitiert haben [10].

In der oben erwähnten Phase III Studie, wurde durch Ibritumomab Tiuxetan als Konsolidierungstherapie im Vergleich zu keiner Konsolidierungstherapie das mediane progressionsfreie Überleben (PFS) um beträchtliche 2 Jahre verlängert. Zusätzlich konnte in 77% der PatientInnen, bei denen nach der Induktionstherapie nur eine Teilremission (PR) erzielt worden war, eine komplett Remission (CR/CRU) erreicht werden. Ähnliche Ergebnisse wurden auch in einer Subgruppen-Analyse gefunden, in der Patienten einerseits nach Therapieansprechen auf die initiale Chemotherapie und andererseits nach Art des verabreichten Chemotherapieregimes stratifiziert wurden.

**trotz europäischer Marktzulassung in 2008, keine breite Anwendung in Österreich**

**progressionsfreies Überleben um etwa 2 Jahre verlängert**

**häufigste Nebenwirkungen waren transiente hämatologische Reaktionen**

**Therapieregimes für FL beinhalten meist Rituximab**

**klinischer Nutzen von Ibritumomab Tiuxetan nach Rituximab Induktionstherapie nicht nachgewiesen**

Die am häufigsten beobachteten unerwünschten Nebenwirkungen waren transiente hämatologische Reaktionen, die, wenn auch schwerwiegend, durch konservative Maßnahmen beherrschbar waren. Unklar hingegen bleiben potentielle, durch Strahlungsschäden verursachte Langzeitfolgen, wie etwa die Entstehung myelodysplastischer Syndrome oder akuter myeloischer Leukämien [18]. Möglicherweise bedingt durch die relative kurze Beobachtungsdauer der Studie sind Daten zu verbesserter Überlebensdauer ausständig. Keine Unterschiede zwischen den beiden Gruppen wurden auch in Bezug auf Lebensqualität oder Schmerzsymptomatik gefunden.

Obwohl diese Studie nicht darauf ausgerichtet war, signifikante Unterschiede zwischen den einzelnen Chemotherapieregimes nachweisen zu können, so wurden doch PFS Ergebnisse für die einzelnen Subgruppen präsentiert. Wie erwähnt, konnte Ibritumomab Tiuxetan in Kombination mit den meisten Therapieregimes bessere Ergebnisse erzielen, als die Vergleichsgruppe. Für die relative kleine Gruppe von PatientInnen (insgesamt 59 Personen), die mit einer Rituximab Erstlinien-Therapie behandelt worden waren, zeigte sich jedoch kein Unterschied hinsichtlich PFS. Da aber moderne therapeutische Strategien zur Behandlung von FL durchwegs Rituximab inkorporieren, bleibt der klinische Nutzen von Ibritumomab Tiuxtan nach einer Rituximab beinhaltenden Induktionstherapie unklar [10]. Mögliche Konsequenz ist einerseits, dass mit Rituximab vorbehandelte PatientInnen von der zusätzlichen Verabreichung von Zevalin® profitieren, oder aber, dass lediglich höhere Kosten und vermehrte Nebenwirkungen entstehen, diese aber nicht in zusätzlichem klinischen Nutzen für PatientInnen resultieren.

Zusätzlich zu weiteren Studien, die den Einsatz dieser Kombination recht fertigenden, ist auch der Vergleich *zwischen* den beiden Substanzen von Interesse: da mit Rituximab als Erhaltungstherapie ebenfalls vielversprechende Resultate erzielt werden konnten [19], stellt sich nun die Frage, ob der Kon solidierungstherapie mit Ibritumomab Tiuxtan oder der Erhaltungstherapie mit Rituximab der Vorzug gegeben werden sollte [8, 10]. Allerdings könnte Ibritumomab Tiuxetan in Zukunft auch als Erstlinien-Therapie zum Einsatz kommen – diesbezügliche Studien sind bereits im Gange. Daneben wird der Einsatz von Zevalin® bei anderen B-NHL Subtypen und klinischen Situationen untersucht. Eine wichtige Rolle könnte in Zukunft auch der Einsatz bei PatientInnen, die für eine prolongierte konventionelle Chemotherapie ungeeignet sind, spielen.

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