RELAPSED FOLLICULAR LYMPHOMA SEQUENTIALLY TREATED WITH RITUXIMAB AND ⁹⁰Y-IBRITUMOMAB TIUXETAN. CASE REPORT

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Background: Monoclonal antibodies have dramatically changed the treatment possibilities for follicular lymphoma. ⁹⁰Y-ibritumomab tiuxetan (Zevalin®) is the first radioimmunotherapy agent approved for the treatment of relapsed and resistant follicular lymphoma patients. Long-term benefit was observed especially for patients achieving CR after radioimmunotherapy.

Methods and Results: A 65-year-old female patient with the second relapse of CD20 positive follicular lymphoma and multiple concomitant diseases was treated with four weekly doses of rituximab (375 mg/m²). ¹⁸F-fluoro-deoxy-glucose positron emission tomography combined with computed tomography (PET-CT) demonstrated only partial response to therapy with persistent PET scan positivity in enlarged abdominal lymph nodes. Therefore, it was decided to treat her with a 1200-MBq (32-mCi) dose of ⁹⁰Y-ibritumomab tiuxetan radioimmunotherapy. No acute complications were noted afterwards. Hematological nadirs were reached 4 weeks later, with a platelet count of 24x10⁹/l that normalized within the next 2 weeks. The patient had neither infection nor bleeding complications. Eight weeks after radioimmunotherapy, the PET-CT scans documented only 3 lymph nodes around the abdominal aorta, maximum size 2x1 cm. The PET scan analysis proved no accumulation of ¹⁸F-fluoro-deoxy-glucose in any lymph nodes or other organs and tissues.

Conclusions: Sequential treatment with rituximab and ⁹⁰Y-ibritumomab tiuxetan may be an interesting alternative in cases of relapsed follicular or other indolent lymphomas in pretreated or older patients with other concomitant diseases.

INTRODUCTION

Follicular lymphoma (FL) is the second most frequent non-Hodgkin's lymphoma (NHL) in Europe and the USA. Despite good responsiveness to chemotherapy, most responses are incomplete and temporary, with patients relapsing from their lymphomas irrespective of which conventional regimen is administered. With standard chemotherapy, the median survival ranges from 8 to 10 years, and the prognosis of FL remained largely unchanged over the last decades of the 20th century¹. Recently, new treatment modalities have been developed. These include monoclonal antibodies (MAb) that have dramatically changed FL treatment possibilities. The only currently available unconjugated monoclonal antibody with proven activity in FL is rituximab – a chimeric anti-CD20 MAb. A pilot phase II study demonstrated significant activity of once-weekly rituximab at a dose of 375 mg/m² administered for 4 weeks to previously treated FL patients². The intent-to-treat response rate was 56% according to standard

response criteria and the median time to progression in responding patients was 13.0 months. In spite of these promising results, it is evident that the response duration is limited. The response rate and therapeutic benefit of the naked anti-CD20 MAb can be enhanced by using conjugated monoclonal antibodies. Radiolabeled antibodies seem to be an appealing option because lymphoma cells are generally sensitive to radiotherapy. Radioimmunotherapy (RIT) is attractive due to its so-called cross-fire effect, damaging target and neighboring tumor cells including antigen-negative cells as well as those to which the antibody is unable to gain access. ⁹⁰Y-ibritumomab tiuxetan was the first RIT agent approved for the treatment of relapsed and resistant FL patients^{3,4}. It is a murine IgG₁ kappa anti-CD20 MAb covalently bound to tiuxetan, which chelates the radioisotope ⁹⁰Y. This emits pure beta radiation over a radius of approximately 100–200 cells which allows sufficient cross-fire effect with no special isolation or protection procedures required. In a phase III randomized trial, ⁹⁰Y-ibritumomab tiuxetan was compared directly

Fig. 1. Fused positron emission tomography/computed tomography scans documenting enlarged lymph nodes sized 4x3 cm around the abdominal aorta strongly accumulating ^{18}F -fluoro-deoxy-glucose – the status after rituximab therapy.

Fig. 2. Fused positron emission tomography/computed tomography scans documenting lymph nodes around the abdominal aorta with the maximum size of 2x1 cm and physiological ^{18}F -fluoro-deoxy-glucose distribution – the status after ^{90}Y -ibritumomab tiuxetan therapy.

with rituximab in the treatment of relapsed or refractory low-grade, follicular or transformed NHL⁵. The overall response (OR) and complete remission (CR) rates were significantly higher with RIT (OR 83 % vs 56 %, $p = 0.002$; CR 30 % vs 16 %, $p = 0.004$) and the trend towards a longer median duration of response was observed especially for patients with follicular histology (18.5 months vs 12.1 months, $p = 0.371$). Long-term benefit was observed for patients achieving CR after RIT and some responses continue for more than 3 years.

The sequential rituximab immunotherapy and ^{90}Y -ibritumomab tiuxetan RIT may be an interesting approach to improving OR and prolonging survival in relapsed, heavily pretreated or older FL patients. Here we report the case of a 65-year-old female with FL who was successfully treated with rituximab and subsequently with ^{90}Y -ibritumomab tiuxetan.

CASE REPORT

The patient was diagnosed with grade II FL in 1998 (at 57 years of age), the neoplastic cells were positive for BCL-2/IgH gene rearrangement detected by polymerase chain reaction. The disease was staged as IIIB, according to the Ann Arbor staging system, with cervical, axillary, abdominal, iliac (the largest node 5x4 cm) and inguinal lymphadenopathy (the largest node 6x4 cm) causing massive lymphedema of the right leg. Bone marrow aspiration and biopsy showed no lymphoma cells. A complete blood count was in the normal range in all parameters. Other laboratory studies also displayed normal values of the main biochemical parameters including lactate dehydrogenase. Only beta-2 microglobulin was abnormally high (3.98 mg/l). The international prognostic index (IPI) was 1, follicular lymphoma IPI (FLIPI) was retrospectively counted as 2. Treatment with 6 cycles of cyclophosphamide, doxorubicine, vincristine and prednisone (CHOP) induced complete remission in January 1999. Unfortunately, the remission only lasted for 9 months and the patient relapsed in right inguinal lymph nodes (LNs) (5x3 cm), with recurrent leg lymphedema. She received 4 cycles of fludarabine, mitoxantrone and dexamethasone (FND) and after completion of chemotherapy she underwent involved field radiotherapy (40 Gy) targeted to the right inguinal region. Complete remission was confirmed by computed tomography (CT) in May 2000. Then the patient was carefully observed but she gradually developed acute pancreatitis progressing to a chronic form, essential hypertension (WHO grade II), non-insulin dependent diabetes mellitus, chronic pyelonephritis with repeated acute urinary infection and chronic pharyngitis.

In February 2006, we diagnosed the second relapse of lymphoma in the right inguinal, pelvic and abdominal LNs (multiple LNs, maximum size 5x3 cm), the patient suffered from B-symptoms. Histopathological analysis of extirpated inguinal LN demonstrated no evidence of lymphoma transformation, the CD20 antigen was strongly expressed. The bone marrow was still negative. In April

2006, we decided to administer four weekly doses of rituximab (375 mg/m²) and dexamethasone (20 mg/m²), with respect to the patient's age, concomitant diseases and her concerns about chemotherapy complications. Rituximab infusions were well tolerated and 4 weeks after the last dose, positron emission tomography (PET) combined with CT examination was carried out. The CT scans showed nine enlarged LNs (the largest LN size 4x3 cm) around the abdominal aorta that strongly accumulated ^{18}F -fluorodeoxy-glucose (^{18}F -FDG), in the PET scans, the pelvic and inguinal LNs completely regressed (Fig. 1). Considering the PET-CT results, good tolerance of rituximab, no bone marrow involvement and normal blood cell count, we opted for ^{90}Y -ibritumomab tiuxetan therapy (June 2006). The patient was fully informed about the principles and possible adverse effects of radioimmunotherapy and she agreed with this treatment modality. At day 1, an intravenous infusion of rituximab (250 mg/m²) was administered and one week later (day 8), the same rituximab infusion dose was followed by short i.v. application of ^{90}Y -ibritumomab tiuxetan in a dose of 1200 MBq (32 mCi), at the department of nuclear medicine. No acute complications were noted and the patient was discharged and followed on an outpatient basis. Hematological nadirs were reached 4 week later, with the platelet count $24 \times 10^9/\text{l}$, white blood cell count $3.6 \times 10^9/\text{l}$ and neutrophil count $2.0 \times 10^9/\text{l}$. The platelet count normalized within the next 2 weeks, the patient had neither infection nor bleeding complications and felt very comfortable. Eight weeks after radioimmunotherapy, another PET-CT examination was performed. The CT scans documented only 3 LNs around the abdominal aorta with the maximum size of 2x1 cm, the PET analysis proved only physiological ^{18}F -FDG distribution with no accumulation of the radioactive substance in any LNs (Fig. 2). The final treatment result was assessed according to the standard response criteria as PET-negative unconfirmed complete remission (CRu). Eight months after radioimmunotherapy, the patient was subjectively well, clinically in durable disease remission without any late complications or worsening of the concomitant diseases.

CONCLUSIONS

Sequential treatment with rituximab and ^{90}Y -ibritumomab tiuxetan may be a feasible alternative in cases of relapsed follicular or other indolent lymphomas in pretreated or older patients with other concomitant diseases. Rituximab "induction" probably reduces tumor burden and the subsequent application of ^{90}Y -ibritumomab tiuxetan "consolidation" can effectively eradicate the remaining lymphoma sites. Maintenance rituximab therapy after achieved remission could be another possible strategy for prolonging a patient's disease- or progression-free survival.

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REFERENCES

1. Hiddemann W, Buske C, Dreyling M, Weigert O, Lenz G, Unterhalt M: Treatment Strategies in Follicular Lymphomas: Current Status and Future Perspectives. *J. Clin. Oncol.* 2005; 23:6394–6399.
2. McLaughlin P, Grillo-Lopez AJ, Link BK, Levy R, Czuczman MS, Williams ME, et al.: Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: Half of patients respond to a 4-dose treatment program. *J. Clin. Oncol.* 1998; 16:2825–2833.
3. Knox SJ, Goris ML, Trisler K, Negrin R, Davis T, Liles TM, et al.: Yttrium-90-labeled anti-CD20 monoclonal antibody therapy of recurrent B-cell lymphoma. *Clin. Cancer Res.* 1996; 2:457–470.
4. Witzig TE, White CA, Wiseman GA, Gordon LI, Emmanouilides C, Raubitschek A, et al.: Phase I/II trial of IDEC-Y2B8 radioimmunotherapy for treatment of relapsed or refractory CD20+ B-cell non-Hodgkin's lymphoma. *J. Clin. Oncol.* 1999; 17:3793–3803.
5. Witzig TE, Gordon LI, Cabanillas F, Czuczman MS, Emmanouilides C, Joyce R, et al.: Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. *J. Clin. Oncol.* 2002; 20:2453–2463.
6. Gordon LI, Molina A, Witzig T, Emmanouilides C, Raubitschek A, Darif M, et al.: Durable responses after ibritumomab tiuxetan radioimmunotherapy for CD20+ B-cell lymphoma: long-term follow-up of a phase 1/2 study. *Blood* 2004; 103:4429–4431.