Unexpected outcome (positive or negative) including adverse drug reactions

Durable complete remission in a patient with recurrent DLBCL receiving rituximab monotherapy after high-dose chemotherapy and autologous stem cell transplantation

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Summary

The optimal management of patients with diffuse large B cell lymphoma relapsing after autologous haematopoietic stem cell transplantation (HCT) is difficult and no standard treatment has been defined. The authors here report the case of a rituximab-naïve patient who relapsed after HCT and was cured with rituximab monotherapy.

BACKGROUND

We feel that the clinical course of this patient is of particular interest, as it highlights the potency of rituximab monotherapy in rituximab-naïve patients highly refractory to chemotherapy including high-dose therapy with autologous stem cell transplantation.

CASE PRESENTATION

A 57-year-old man with generalised lymphadenopathy, splenomegaly and B symptoms was admitted to the hematology ward for further evaluation in 2000. The diagnostic investigation identified a diffuse large B cell lymphoma (DLBCL) stage IVB, IPI 3 with 80%–90% bone marrow infiltration by large lymphocytes expressing CD20 and CD79a with prominent and cleaved nuclei (cytogenetics was normal, no fluorescence insitu hybridisation was performed at this time). The Eastern Cooperative Oncology Group (ECOG) performance status of this patient was 1 and besides an asymptomatic HBs antigen carrier status the medical history was uneventful. As initial treatment he received six cycles of CHOP therapy (cyclophosphamide, doxorubicine, vincristine and prednisone) and consequently attained a complete remission. Six months after first line chemotherapy, the patient again experienced B symptoms and CT revealed a nodal relapse and liver lesions. Recurrent disease was histologically confirmed by liver biopsy. The patient subsequently received salvage-chemotherapy with four cycles of DHAP (dexamethasone, cisplatin, cytarabine) including successful stem cell mobilisation and cryopreservation after the third cycle. Again, he achieved a complete remission as shown by a normal CT-scan and lymphoma-free bone marrow trephine biopsy and was referred to a consolidating autologous stem cell transplantation after conditioning with BEAM (carmustine, etoposide, cytarabine, melphalan). Already 6 months after transplantation the patient experienced his second relapse with a disease pattern similar to that of his first relapse. The CT-scan showed

recurrent lymphadenopathy up to 5×2 cm, pronounced splenomegaly with diffuse lymphoma infiltration as well as hepatic involvement. At this time point the patient was not willing to perform the recommended re-biopsy and refused any further diagnostic or therapeutic procedure. However, as clinical symptoms worsened, after 1 month another CT-scan was performed, showing further progressive lymphadenopathy now up to 9×6 cm (figure 1A,B) as well as progressive liver and spleen involvement. Epstein–Barr virus (EBV) and cytomegalovirus serology and PCR remained negative, excluding these viruses to be responsible for lymphadenopathy. Moreover, from a clinical perspective granulomatous diseases, such as sarcoidosis or tuberculosis were rather unlikely, as the CT-scan, increased lactate dehydrogenase did not support that these diseases were responsible for the observed lymphadenopathy. Thus, disease recurrence of DLBCL was the most probable diagnosis. Of note, the patient at that time-point denied any further intensive chemotherapy but agreed to be treated with single agent rituximab, which at that time was not licensed in Austria. Of note, during the first infusion, the patient experienced extensive shivering and high fever consistent with a grade 3 cytokine release syndrome despite adequate premedication. He subsequently received six times rituximab 375 mg/m² in weekly intervals which were well tolerated. Unexpectedly, 4 weeks after the first rituximab infusion, the patient already achieved a complete reversion of lymphadenopathy as well as the diffuse infiltration of liver and spleen as assessed by CT- and positron emission tomography-scan (which was not performed before). Due to this unusual course of the disease we decided to continue with rituximab maintenance therapy for 2 years in 3-monthly intervals under concurrent lamivudine prophylaxis. Despite the disappearance of enlarged lymph nodes as well as hepatic and splenic infiltrates, persisting splenomegaly (20×15×8 cm) was detectable throughout rituximab maintenance. Therefore, surgical splenectomy was performed

Figure 1 Response evaluation by CT-scan showed already 6 months after haematopoietic stem cell transplantation recurrent lymphadenopathy (arrows) and splenomegaly with diffuse infiltration (asterisk) (A and B). After application of rituximab monotherapy complete remission was reported and persisted for 10 years until now (C: reduction of left hilar lymph nodes and retrosternal mass, D: resolved retroperitoneal lymphadenopathy, postsplenectomy).

(figure 1D). Surprisingly, despite an extensive histopathological investigation the spleen was lymphoma-free, thus confirming ongoing complete remission.

DIFFERENTIAL DIAGNOSIS

As differential diagnosis EBV associated proliferation-disease should be considered and also other granulomatous diseases like sarcoidosis or tuberculosis. In this case EBV serology and also PCR were negative excluding EBV associated disease. The radiological pattern and also the clinical symptoms were typical for recurrent DLBCL.

OUTCOME AND FOLLOW-UP

Currently, that is, almost 10 years after the initiation of single agent rituximab the patient remains still in complete remission and may thus be considered cured.

DISCUSSION

This case of a chemotherapy-refractory patient with DLBCL achieving cure with single-agent rituximab after failure of autologous HSCT is particularly interesting as prognosis for patients with DLBCL experiencing relapse after autologous transplantation is dismal. In rare, selected cases ongoing complete remissions up to 32 months after single agent rituximab have been described.¹ However, although early trial data from patients with DLBCL (n=54) in first or second relapse treated with rituximab monotherapy reported response rates of 31 per cent (including 9% complete remissions), progression-free survival rarely exceed 11 months.² Moreover, Pan *et al* reported on the use of single agent rituximab in patients (n=17) suffering from aggressive non-Hodgkin's lymphomas (NHLs) whose disease was refractory to, or relapsed after autologous stem cell transplantation.³ Overall response rate was 53% including four patients (23%) achieving a complete

remission. But again, median progression-free survival was limited with 13 months for responders.

In contrast to these data derived from the prerituximab era, the expected response rates in already rituximab pretreated patients are markedly lower. As an example, data from the Collaborative Trial in Relapsed Aggressive Lymphomas (CORAL) study evaluating different rituximab containing salvage regimens (R-DHAP vs R-ICE; ifosfamide, etoposide and carboplatin) in primary refractory or relapsed DLBCL followed by high dose chemotherapy and autologous haematopoietic stem cell transplantation (HCT) showed that patients with disease recurrence within 12 months not having received initial rituximab had a significantly prolonged 3-year event-free survival.⁴ Accordingly, the Groupe d'Etude des Lymphomes de l'Adulte (GELA) study showed a significant benefit of a rituximab-containing salvage therapy only in rituximab-naïve patients.⁵ A retrospective analysis by Martin *et al*⁶ even suggests an independent adverse prognostic impact of rituximab pretreatment before HCT for progression free survival (rituximab naïve patients 57% at 3 years compared with rituximab pretreated 17%) and overall survival (rituximab naïve patients 67% at 3 years compared with 38% after rituximab pretreatment). Therefore and despite the undisputed value of rituximab for DLBCL first-line treatment, its role in the relapsed and refractory setting is controversial, because most of the studies enrolled patients of whom the major proportion had not received previous rituximab. For example, the study by Vellenga *et al*⁷ randomised 239 patients with relapsed aggressive NHL to DHAP-based combination chemotherapy with or without rituximab. In this patient population only 4 per cent had received rituximab upfront. The authors showed that the combination of chemotherapy with rituximab resulted in significant higher response rates and higher rates of failure-free survival. The biological basis for this observation remains elusive so far,

as most recurrent lymphomas still express CD20 after having received rituximab upfront.⁸ This observation suggests a selection process of rituximab-resistant lymphoma cells, which is not due to loss of the target antigen, but rather affects intracellular signaling components.^{9 10}

In summary, our case particularly underscores the therapeutic value of rituximab monotherapy in recurrent rituximab-naïve patients with DLBCL, even though these patients are now rare due to the fact that rituximab has an undisputed value in the first-line treatment of DLBCL.^{11 12}

Learning points

- ▶ Currently, only allogeneic stem cell transplantation is considered a curative approach in diffuse-large cell lymphoma patients with recurrent disease after high-dose chemotherapy and autologous stem cell transplantation.
- ▶ Rituximab monotherapy represents a potent treatment option for rituximab-naïve patients highly refractory to chemotherapy including high-dose therapy with autologous stem cell transplantation.
- ▶ The mechanisms of reduced rituximab-sensitivity in previously rituximab-exposed patients are not exactly defined.

Competing interests None.

Patient consent Obtained.

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