Peer reviewed article

Delayed-onset and long-lasting severe neutropenia due to rituximab

Silvia Hofer, Romaine Viollier, Christian Ludwig

Department of Medical Oncology, St. Claraspital, Basel, Switzerland

Summary

Background: Rituximab, a monoclonal antibody, is effective in CD20-positive B-cell lymphoma and is now widely used either as a single agent or in combination with chemotherapy. The antibody's toxicity is generally mild and transient. There are reports of protracted neutropenia in patients treated with rituximab.

Case report: We report on a patient with Burkitt's lymphoma treated with the hyper-CVAD chemotherapy regimen combined with rituximab. Four weeks after the five months' treatment marked neutropenia and hypogammaglobulinaemia occurred and persisted for one year. Both laboratory findings were not associated with severe infections in our patient.

Conclusions: Delayed-onset neutropenia is a newly recognised toxicity of rituximab treatment which may last up to one year and be complicated by serious infections.

Key words: rituximab; mabthera; neutropenia; hypogammaglobulinaemia; Burkitt's lymphoma

Introduction

Monoclonal antibody therapy with the anti-CD20 antibody rituximab has already had an enormous impact on the treatment of B-cell lymphoma and autoimmune disorders. The treatment is generally safe and well tolerated and exhibits little interaction with conventional chemotherapies. However, there are some special toxicities which were recognised only in the postmarketing period.

Case report

A 30-year-old HIV-negative male was diagnosed with intestinal CD20-positive Burkitt's lymphoma and retroperitoneal lymphadenopathy. Treatment with the Hyper-CVAD regimen in combination with rituximab for eight courses over a five months' period was initiated. Hyper-CVAD consists of cyclophosphamide, vincristine, doxorubicin, dexamethasone, high dose methotrexate and ara-C [1, 2]. Granulocyte colony stimulating factor (GCSF) was initiated 24 hours after each chemotherapy cycle until the total white blood count was >3×10⁹/L. Complete remission of Burkitt's lymphoma was documented by repetitive CT-scans and FDG-PET imaging. Four weeks after the last cycle of combined chemotherapy and rituximab, severe neutropenia developed and persisted for a year. Hypogammaglobulinaemia and subnormal IgG levels were concurrently documented (Figure 1). No serious infection occurred during this period except for several upper respiratory tract infections in wintertime. GCSF treatment of delayed onset neutropenia was not attempted in our patient since only temporary benefit was expected. Bone marrow aspiration obtained one and two months after the onset of neutropenia disclosed hypocellular findings with a marked reduction in mature neutrophils and neutrophil precursors. Viruses known to cause neutropenia were ruled out by PCR. Antibodies bound to the surface of neutrophils were not assessed in our patient. The neutropenia resolved spontaneously and Burkitt's lymphoma remains in complete remission (FDG-PET, cytogenetics) at one year after combined treatment.

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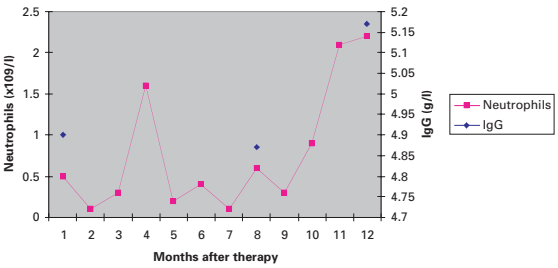

Tc x10⁹/l	174	185	179	200	155	183	169	156	150	146	167	161
Hb g/l	118	127	133	127	128	134	139	133	131	134	132	137
Months after therapy	1	2	3	4	5	6	7	8	9	10	11	12

Figure 1

Neutrophils and serum IgG after chemotherapy and rituximab.
Normal values: IgG: 7.0–16.0 g/l; haemoglobin (male): 120–160 g/l; thrombocytes: 150–400 × 10⁹/l. NCI common toxicity criteria for neutropenia: grade 1: 1.5–2 × 10⁹/l; grade 2: 1–1.5 × 10⁹/l; grade 3: 0.5–1 × 10⁹/l; grade 4: <0.5 × 10⁹/l.

Discussion

It is well known that rituximab reversibly depletes normal B-lymphocytes and occasionally leads to hypogammaglobulinaemia. Recovery is expected within one year [5]. During recovery the acquisition of a new immune repertoire has been described [8]. In the pivotal studies single agent rituximab was associated with delayed onset neutropenia NCI grade 3–4 in up to 8% [5]. Higher numbers are reported with rituximab and chemotherapy. In the transplant setting delayed onset neutropenia following rituximab has been observed in up to 43–54% [7–9]. Marked hypogammaglobulinaemia is often associated with this finding [5, 7, 8, 10]. Delay after the last infusion of rituximab to the nadir of neutrophils is reported to range from several weeks to some months [3, 4, 8, 9]. Pancytopenia is rarely observed [4, 7, 8]. Serious infections are reported in some series, whereas in others neutropenia did not result in complications [4, 5, 8]. Neutrophil counts recovered spontaneously (as in our case) or responded to GCSF and/or intravenous immunoglobulin (IVIG) treatment [6–8, 10].

The aetiology of delayed-onset neutropenia is not clear. Several hypotheses have been advanced, such as transient production of autoantibodies against neutrophils during immune reconstitution [3, 4, 8, 9] or viral infection during dysfunctional humoral immunity, A direct effect of rituximab seems unlikely, since granulocytes and hematopoietic precursor cells do not express CD20 and the circulating half-life of rituximab is known to last from several days to one week [5].

As exposure to rituximab is increasing worldwide, delayed-onset neutropenia is a condition which should be recognised. Infections occurring during delayed-onset neutropenia, even in combination with hypogammaglobulinaemia, are usually minor; however, in view of the risk of sepsis such neutropenic episodes cannot be considered harmless events. Treatment with G-CSF or IVIG has been effective and needs further evaluation.

Correspondence:
Silvia Hofer
Department of Medicine
St. Claraspital
CH-4016 Basel
Switzerland
E-Mail: silvia.hofer@claraspital.ch

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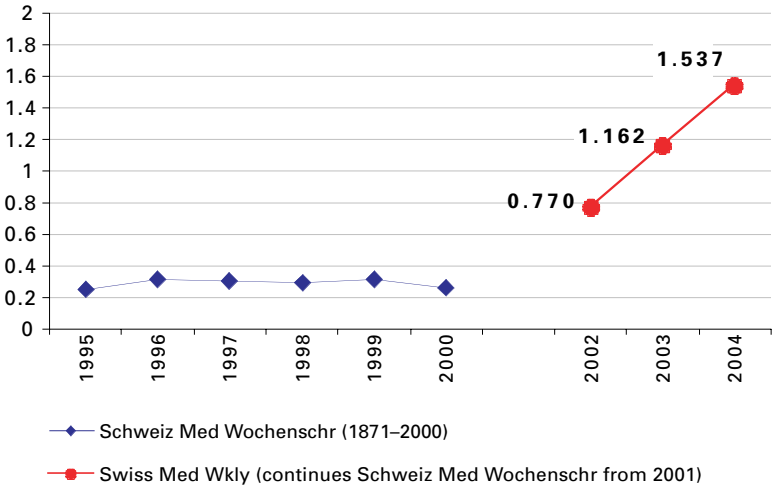

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