Leukemia Research Reports 9 (2018) 16–17

Contents lists available at ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

Subcutaneous rituximab given to patients for other indications than CD20 + B-cell lymphoma: A monocentric study of 20 cases

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ARTICLE INFO

Keywords:
Subcutaneous rituximab /other indications than B-lymphoma

1. Introduction

Rituximab (R) (Rituxan®, Roche, Basel Switzerland) is the first anti-CD20 monoclonal antibody that has demonstrated efficacy in patients with various lymphoid malignancies, including indolent and aggressive forms of B-cell non-Hodgkin's lymphoma and B-cell chronic lymphocytic leukemia [1]. Administered intravenously (IV), it has been shown to be also efficient to treat other hematologic situations such as EBV reactivation, especially after hematopoietic stem cell transplantation (HSCT), [2] or ITP [3]. Finally, survivals of younger patients with CD20-positive Philadelphia-negative ALL are significantly increased when combining IV-R with chemotherapy [4].

Recently, a subcutaneous (SC) formulation of R (Rituxan Hycela™, rituximab and hyaluronidase human, Roche, Basel, Switzerland) has been approved by FDA for B-cell lymphoma. SC-R includes the same monoclonal antibody as intravenous rituximab in combination with hyaluronidase human, an enzyme that helps to deliver rituximab under the skin. Clinical studies have demonstrated that subcutaneous administration of SC-R resulted in non-inferior levels of rituximab in the blood and comparable clinical efficacy outcomes compared to IV-R [1]. It provides a highly-concentrated fixed dose of rituximab with the advantages of reducing treatment times and nursing workload [5] and potentially providing greater comfort and convenience for patients [6] and lesser dosing errors, shorter preparation time or reduced drug wastage for pharmacy dispensers. However, patients can currently only receive SC-R after at least one full dose of IV-R and premedication. The most common (≥20%) adverse reactions observed with SC-R are infections, neutropenia, nausea, constipation, cough and fatigue, alopecia, nausea and erythema at the injection site. At our knowledge, there is no published data addressing the tolerance and the efficacy of SC-R given to patients with other indications than CD20+ B cell lymphoma. As a consequence, we have retrospectively analyzed all cases who received at our center (University Hospital of Nantes, France) at least one dose of SC-R but with no lymphoma indication.

2. Methods

Three situations were considered: EBV reactivation (post transplantation or not), ITP or ALL treatment. All patients received their first (s) dose(s) of R IV (375 mg/m2/injection) and a switch to SC-R (1400 mg/injection) was realized only if they didn't experience grade 3 or 4 adverse event (AE) with IV formulation. Our rules is to provide R (IV + SC) weekly, up to 4 doses for ITP (in case of platelets counts < 30 Giga/L with no response to corticosteroids or immunoglobulin) and EBV reactivation (in case of 2 positive PCR > 4 log10 number of viral DNA copies), while GRAALL schedule [4] is followed for R administration in CD20+ ALL patients. A premedication with antipyretic, antihistamine and corticosteroid was systematically administered before every infusion. Tolerance of SC-R was appreciated using National Cancer Institute Common Terminology Criteria for Adverse Events v4.03 and any grade 3 or 4 AE related to SC-R was sufficient to stop treatment. Late-onset neutropenia (LON) was defined as neutropenia developing at least three to four weeks following the end of SC-R administration despite a previous normal neutrophil count [7]. Success of SC-R was defined by either a documentation of a negative EBV PCR or absence of ALL relapse or platelets counts reaching at least 100 Giga/L.

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https://doi.org/10.1016/j.lrr.2018.01.002
Received 8 December 2017; Accepted 12 January 2018
Available online 17 January 2018

3. Cases report

Between February 2016 and June 2017, 20 patients (male n = 17) with a median age of 60 years old (range: 33–76) received SC-R in our institution. Overall, 102 R including 58 SC-R were administered with a median of 3 R (range: 2–26) and 2 SC-R (range: 1–16) injection per patient, respectively. No patients switched back to IV formulation. The median follow-up from the last SC-R administration was 4.4 months (range: 0.2–11.2 months).

No grade 3/4 infusion related reaction were documented in this series while 4 out of 16 assessable cases presented with LON at a median of 45 days (range: 44–70) after the last SC-R injection. Neutropenia lasted a median of 6 days (range: 4–9) with the help of GCSF and was not responsible for complication.

Eleven cases received SC-R for EBV reactivation (including 8 after allogeneic transplant and 3 in a context of aplastic anemia) with a median of 3 R (IV + SC, range: 1–4) and 2 SC-R (range: 1–3) injections. One patient died of concomitant invasive fungal infection and was not evaluable for efficacy. All of the ten other patients were documented with negative EBV PCR after treatment. Four patients received SC-R during ALL first line treatment with a median of 11 R (IV + SC, range: 3–26) and 6 SC-R (range: 1–16) injections. Two patients have received more than the number of R infusion scheduled (17 and 26) because of high toxicity related to the chemotherapy and it was chosen to deliver a maintenance therapy with vincristine/SC-R and prednisone. None of the four ALL patients had relapsed so far at 2, 8, 18 and 20 months from diagnosis with a median follow-up of 13 months (2–20). Five patients received SC-R for ITP (including 3 after allogeneic transplant) with a median of 3 R (IV + SC, range: 3–4) and 2 SC-R (range: 1–3) injections. Three patients obtained platelets count improvement within a median of 28 days (19–48) and none relapsed so far.

4. Conclusion

Our study is the first to address the feasibility of SC-R in other populations than CD20 + B-Cell lymphoma patients. SC-R seems to demonstrate a comparable efficacy/safety profile as IV-R. LON incidence was comparable with previous reports [8]. A costing study should be envisaged to demonstrate cost saving as it is the case for diffuse large B-cell lymphoma [9]. Finally, it may be possible to give the first dose subcutaneously rather than intravenously, even without premedication, as it was reported recently for lymphoma cases [10]. We conclude that there should be no restriction to use SC-R for these patients in the future as it may improve quality of care from both side point-of-view, patient and health providers.

Clinical practice points

- Subcutaneous formulation of R rituximab seems to be effective to treat other populations than CD20 + B-Cell lymphoma patients, i.e. treatment of Epstein-Barr virus (EBV) reactivation, immune thrombocytopenic purpura (ITP) or CD20 + Philadelphia-negative acute lymphoblastic leukemia.
- No grade 3/4 infusion related reaction were documented in this series

Conflicts of interest

The authors report no conflicts of interest.

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