Rituximab dosing in B cell lymphoma

Yazeed Sawalha, Mitchell R. Smith

Department of Medical Oncology and Hematology, Taussig Cancer Institute, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA

Correspondence: Mitchell R. Smith
E-mail: smithm14@ccf.org
Received: October 24, 2016
Published online: December 05, 2016

Rituximab has been extensively used in the treatment of CD20-expressing B cell neoplasms in the last two decades. Despite that, its dose and scheduling are still being questioned as they are inadequately supported by data. Our retrospective study of patients with indolent B cell lymphoma showed that older males and patients with higher weight had worse outcomes when treated with first line rituximab-containing chemotherapy, probably due to faster rituximab clearance. This suggests that a subset of patients with indolent B cell lymphoma may be sub-optimally dosed with rituximab as commonly administered. These results are in line with other studies in aggressive lymphoma where rituximab pharmacokinetics were shown to be affected by gender, age and weight and can affect outcomes. Our study also highlights the challenge of presenting the newer anti-CD20 monoclonal antibodies as intrinsically superior to rituximab when they are given at higher dose and more frequent administration.

Keywords: rituximab; monoclonal antibodies; B cell lymphoma; dosing; pharmacokinetics


Copyright: © 2016 The Authors. Licensed under a Creative Commons Attribution 4.0 International License which allows users including authors of articles to copy and redistribute the material in any medium or format, in addition to remix, transform, and build upon the material for any purpose, even commercially, as long as the author and original source are properly cited or credited.

Rituximab is a chimeric monoclonal antibody (MoAb) that binds the CD20 antigen, a transmembrane phosphoprotein expressed by B-lymphocytes. It induces target cell death through programmed cell death, complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity [1]. Despite the widespread use of rituximab in B cell lymphoma, questions persist regarding optimal dose and scheduling given inadequate supporting scientific evidence. To appreciate that, it is key to understand the history behind the current dosing system and how it is related to rituximab pharmacokinetics (PK).

There are two major pathways for rituximab clearance: CD20-mediated elimination, which is saturable as it is dependent on the tumor mass, and non-specific nonsaturable clearance through proteolysis and non-specific endocytosis by the liver and monocytes/macrophages of the reticuloendothelial system [2]. The total clearance of rituximab decreases markedly with increasing serum rituximab concentrations as the CD20-mediated elimination pathway becomes saturated [2].

The use of rituximab in B cell lymphoma dates back to 1994, when 15 patients with relapsed non-Hodgkin’s lymphoma (NHL) received a single infusion of rituximab in doses ranging from 10 to 500 mg/m² in a phase I clinical trial [3]. Toxicities were limited to grade 1 or 2 infusion reactions with no dose-limiting toxicities identified. This was followed
by another phase I trial of 20 patients with relapsed NHL who received 4 weekly infusions of rituximab in doses ranging from 125 - 375 mg/m² [4]. Even though dose-limiting toxicities were not identified in the 375 mg/m² dose group in either study, and a maximum tolerated dose was not reached, this dose was chosen empirically for further phase II and III trials. In 1997, a phase II multicenter study established the safety and efficacy of 4 weekly infusions of 375mg/m² rituximab in patients with relapsed NHL [5], and rituximab became the first MoAb approved for use in the treatment of cancer.

Rituximab was subsequently shown to be safe and effective when combined with chemotherapy (CTX) (typically given every 3-4 weeks) for the initial treatment of patients with indolent or aggressive B cell lymphoma. This approach prolongs the progression-free (PFS) and overall survival (OS) and is now considered a standard of care [6, 7]. Rituximab as a single agent given at 375 mg/m² weekly for 4 weeks has also been used to treat patients with low tumor burden indolent NHL (iNHL) or those with co-morbidities [8-10]. A 375 mg/m² weekly x 8 week schedule was investigated in a non-randomized trial of patients with relapsed or refractory low-grade lymphoma but did not show improved overall response rate or response duration, and is not commonly used [11].

Given rituximab’s efficacy, long half-life and minimal toxicity, extended treatment or ‘maintenance’ with rituximab has been incorporated into the treatment paradigm of an incurable disease like indolent lymphoma, with different schedules being the subject of several studies. Two separate studies by Hainsworth et al and Hochster et al used 4 weekly doses every 6 months for up to 2 years [12, 13]. This 6 month schedule was based on the observed time to B-cell recovery with rituximab monotherapy [14]. Alternatively, a phase II trial of PK-based maintenance dosing of rituximab showed that a single dose of 375 mg/m² every 3 to 4 months is needed to maintain a ‘therapeutic’ serum level [15]. This concept of therapeutic level was based on PK studies of the pivotal trial showing that the therapeutic response to rituximab in patients with iNHL was associated with serum drug concentration, with responders having higher serum concentrations (median level of 25.4 µg/ml) compared with non-responders (median level of 5.9 µg/ml) [16]. This suggested that a certain serum concentration of rituximab is needed to overcome the effect of tumor burden and the CD20-mediated clearance and has to be reached for maximum anti-lymphoma benefit [16]. The EORTC trial used these data and devised a schedule using 1 infusion every 3 months for a maximum of 2 years [17]. Later, PK data from E4402 trial showed that serum trough levels in nearly half of patients receiving a single rituximab dose every 12 weeks were below the putative 25 mcg/ml threshold [18]. In the PRIMA trial, more than one thousand patients whose indolent lymphoma had responded to rituximab in combination with chemotherapy were then randomized to receive 2 years of rituximab maintenance, 375 mg/m² every 8 weeks, or observation [19]. It is the largest trial to date looking at rituximab maintenance and the first to look at rituximab maintenance after first line rituximab-containing chemotherapy regimens (R-CTX). There has been no direct comparison of these different schedules and all have been shown to be active and well tolerated, but the 8-week schedule is the most commonly used nowadays. The selection of 2 year-duration has been subjective with no strong evidence behind it. There is currently an ongoing clinical trial comparing 2 versus 4 years of rituximab maintenance in patients with iNHL and mantle cell lymphoma (NCT00877214).

Rituximab is similarly dosed at 375 mg/m² when given in combination with CTX (typically every 2-4 weeks) in aggressive B cell lymphoma. However, its PK and the use of alternative dosing regimens have been studied more extensively in patients with diffuse large B cell lymphoma (DLBCL), with data showing that rituximab clearance is strongly affected by weight, age and gender [20]. These data have shown that while young male and female patients had similar rituximab clearances and outcomes, elderly females had slower rituximab clearance, higher serum levels and longer exposure times and subsequently better outcomes compared with elderly males [20, 21]. These age/gender-based variations are possibly related to differences in hepatic enzymatic activity as well as lower cardiac output and hepatic blood flow in females, becoming more noticeable with advanced age [20, 22]. This probably explains the observation that male gender is a poor prognostic factor in elderly patients with DLBCL treated with rituximab, and led to the proposal that the current standard dose and schedule of rituximab for DLBCL are suboptimal [21]. This paved the way for several studies to explore the potential benefits of higher rituximab levels or prolonged exposure time in DLBCL. In the DENSE-R-CHOP-14 study, multiple rituximab doses in the initial cycles achieved higher serum rituximab levels [23]. Although these were not associated with overall differences in event-free survival, the negative prognostic impact of male gender in elderly patients treated with standard rituximab dosing in the RICOVER-60 trial was not seen, suggesting that elderly males benefited from higher serum rituximab levels. In the SMARTERE-R-CHOP-14 study, prolonged rituximab exposure achieved by administering additional doses of rituximab spread over 245 days correlated with improved outcomes in elderly poor-prognosis DLBCL patients, and males benefited considerably more than females [24]. The SEXIE-R-CHOP-14 trial increased rituximab dose
to 500 mg/m² only in elderly male patients treated with six cycles of CHOP-14, whereas females received standard 375 mg/m² [25]. Males achieved higher initial rituximab serum trough levels than females, but their total exposure was similar due to higher clearance. The 3-year PFS and OS between males and females were not significantly different. When males in the SEXIE-R-CHOP-14 trial were compared with age matched males in the RICOVER-60 trial who received 375 mg/m², adjusted for International Prognostic Index (IPI) risk factors, the increased rituximab dose was associated with superior, though not statistically significant, improvement in PFS and OS. Overall, these studies suggest that improved dosing of rituximab may be of clinical benefit in DLBCL. While these data apply to elderly males treated with R-CTX, similar optimization may still be possible for other groups.

Whether this applies to iNHL has been uncertain given the lack of similar trials and data. Our retrospective database analysis of patients with iNHL treated initially with rituximab-based regimens showed that higher weight was associated with worse outcome [26]. In addition, while age and gender independently did not impact outcome, elderly males had worse outcomes compared with elderly females. The poor prognostic associations of weight and of older males in our study were observed only in patients treated with R-CTX, not in those treated with rituximab alone or R-CTX followed by rituximab maintenance. We hypothesize that higher rituximab levels reached with weekly rituximab exceed the putative therapeutic threshold, despite faster clearance, and in fact with weekly administration levels are less affected by altered clearance, nullifying the negative effect of higher weight and male gender. This hypothesis is supported by a study by Coiffier et al. showing no difference in outcomes when 54 patients with various types of NHL were randomized to 8 weekly rituximab infusions at either 375 mg/m² or 500 mg/m² [27], although no PK studies were done. In contrast, as mentioned earlier, in patients with DLBCL treated with R-CTX every 3 weeks, increasing the number of rituximab infusions with initial cycles of CTX or increasing rituximab dose to 500 mg/m² in elderly males tended to overcome the negative prognostic factor of male gender, again implying that altered clearance with rituximab administered every 3 weeks may be clinically relevant [23, 25]. Prolonged exposure attained with maintenance therapy may also lead ultimately to higher trough levels, above the therapeutic threshold. While the duration of maintenance therapy needed to reach the putative therapeutic threshold is not known, most of our patients received the typical 2-year duration. This is supported by the NHL9 study (rituximab, fludarabine and mitoxantrone followed by rituximab maintenance every 2 months for 2 years in follicular lymphoma (FL)), in which women had higher trough rituximab levels, but levels in men did eventually reach those of women by cycle 6 of maintenance [28]. Thus, our male patients probably did eventually attain a therapeutic threshold rituximab level on maintenance. Alternatively, or in addition, maintenance is administered in a setting of lower tumor burden than during induction, which may lead to increased rituximab levels.

Not all patients with CD20-expressing B cell lymphoma respond to rituximab, and many of those who do eventually stop responding. Numerous mechanisms of de novo acquired resistance to rituximab have been described and reviewing them is beyond the scope of this article (reviewed in [29]). However, it is paramount to keep in mind that rituximab PK might play a role in rituximab resistance and that the true potential of rituximab might not be reached at the current dose and schedule. This brings into question the concept of “rituximab-refractory” disease, even though it is a recognized regulatory description. This has become important as several next generation or novel anti-CD20 MoAbs have been developed and are being tested on patients labeled as having rituximab-refractory disease. Ofatumumab and obinutuzumab are the most established, while others including ublituximab and veltuzumab are still under investigation. Ofatumumab is approved in chronic lymphocytic leukemia (CLL) for the treatment of previously untreated fludarabine-ineligible patients [30], and those with fludarabine-refractory disease [31]. It is also approved for extended treatment of patients who are in complete or partial response after at least two lines of therapy for recurrent CLL [32]. It did not show any difference in efficacy compared with rituximab when given with DHAP (cisplatin, cytarabine, dexamethasone) in relapsed or refractory DLBCL [33]. Obinutuzumab showed superior overall response rate, but not PFS, when compared with rituximab in relapsed/refractory iNHL [34]. Of note, this study directly comparing the single agents is one of the few in which they were administered on the same schedule. Obinutuzumab plus bendamustine with obinutuzumab maintenance improved PFS compared with higher dose bendamustine monotherapy with no maintenance in patients with FL who failed to respond or progressed on a previous rituximab-containing regimen [35], resulting in FDA approval for obinutuzumab treatment of this population. Obinutuzumab is also approved, in combination with chlorambucil, for initial treatment of fludarabine-ineligible patients with CLL in whom it improved PFS and molecular response, but not OS, when compared with rituximab–chlorambucil [36]. While the enhanced cytotoxicity of these novel agents seen in vitro studies might explain the better outcome compared with rituximab, they also have been administered at much higher doses and more frequently than the standard dose of rituximab. In the trial of obinutuzumab–chlorambucil versus rituximab–chlorambucil mentioned
above, obinutuzumab was given at a dose of 3000 mg in the first cycle and 1000 mg in subsequent cycles while rituximab was given at a dose of 375 mg/m² in the first cycle and 500 mg/m² in subsequent cycles [36].

A subcutaneous formulation of rituximab (given at a fixed dose of 1400 mg) is currently available and approved for use in Europe for FL and DLBCL. PK studies showed that subcutaneous rituximab was non-inferior to intravenous rituximab and with no new safety concerns [37]. Such an alternative route might offer reduced cost and more convenience for both practitioners and patients.

Randomized clinical trials using different dosing regimens for rituximab are needed. Given the tolerability of rituximab, even at higher or more frequent dosing and with extended therapy, optimizing efficacy should be achievable without significant toxicity. Weight should be reported as a baseline characteristic in antibody-based therapeutic trials and careful attention should be made to underweight and obese patients who may be under-represented.

Conflicting interests

The authors have declared that no conflict of interests exist.

Author contributions

YS and MS wrote the article.

Abbreviations

MoAb: Monoclonal antibody; PK: pharmacokinetics; NHL: non-Hodgkin lymphoma; CTX: chemotherapy; PFS: progression-free survival; OS: overall survival; iNHL: indolent NHL; R-CTX: rituximab-containing chemotherapy; DLBCL: diffuse large B cell lymphoma; FL: follicular lymphoma; CLL: chronic lymphocytic leukemia.

References


