Cancer Chemotherapy and Pharmacology (2019) 84:661–666
https://doi.org/10.1007/s00280-019-03818-1

SHORT COMMUNICATION

Rituximab dosing in hematological malignancies: an old question, revisited

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Received: 2 January 2019 / Accepted: 16 March 2019 / Published online: 21 March 2019

Abstract

Rituximab is the standard of care for most B-cell malignancies. Its rapid clinical development enabled patients to receive this life-prolonging medicine sooner; however, it precluded a thorough assessment of dose selection. Extensive clinical pharmacology data collected from the recent subcutaneous development program enabled re-examination of this old question and support that the approved rituximab dosing regimens in non-Hodgkin's lymphoma and chronic lymphocytic leukemia appear to maximize the clinical benefit in the majority of patients.

Keywords Rituximab · Exposure–response · Dose selection · Monoclonal antibody

Introduction

Initially approved in 1997, rituximab was the first anti-cancer therapeutic monoclonal antibody (Mab) introduced into clinical practice. It is a chimeric Type I Mab that binds to cluster of differentiation 20 (CD20) protein located on the surface of mature B lymphocytes, including malignant B cells, in the majority of patients with mature B-cell lymphomas and leukemias. Upon binding, B-lymphocyte cells are eliminated via immune- and non-immune-mediated mechanisms including complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and induction of apoptosis. Since its approval, rituximab has altered the natural course for hematological malignancies, has become standard of care for many B-cell malignancies, and is classified as a World Health Organization essential medicine [1].

Given its early therapeutic promise, the development and initial approval of rituximab intravenous (IV) was rapid to ensure patients had access. Early clinical studies establishing its dose were limited, and approved doses may not have included comprehensive clinical pharmacological investigations (e.g., exposure–response). Thus, the question on the appropriateness of its dosing regimen has remained for many years. Nonetheless, rituximab has improved survival in patients, and approved rituximab dosing regimens remain backbones of combination therapies. Rituximab IV is approved with a dosing regimen of 375 mg/m^2 in non-Hodgkin's lymphoma (NHL) and 500 mg/m^2 (with first dose of 375 mg/m^2) in chronic lymphocytic leukemia (CLL); with or without chemotherapy.

A subcutaneous (SC) route has been developed, enabling patients to receive rituximab without IV access [2]. The SC development program leveraged the extensive clinical history of rituximab, including knowledge of its pharmacokinetic/pharmacodynamic (PK/PD) relationships, and utilized a PK-based clinical bridging approach to establish the new route. The SC route was founded on the scientific hypothesis that identifying rituximab SC doses (NHL: 1400 mg; CLL: 1600 mg) that achieve exposures (primarily C_{trough}) that are non-inferior to those achieved with the approved IV dosing regimens would result in comparable efficacy and safety to the approved IV doses. This novel approach was a topic of a recent FDA-proposed Oncology Drug Advisory Committee

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(ODAC), and the development program and its results led to a unanimous recommendation for approval [3].

The rituximab SC program collected extensive clinical pharmacology data for both IV and SC routes. Along with the historical experience of rituximab IV, the completed analyses in the context of the rituximab SC development provide one of the largest characterizations of rituximab PK and exposure–response properties throughout its 20 years of clinical experience and by that offer an opportunity to reinvestigate the old question of the approved rituximab dosing regimens. A brief reflection of rituximab PK properties, efficacy and safety, and exposure–response relationships in this context are provided here (see also Roche and FDA ODAC briefing packages [4, 5]). Outcomes support that the approved rituximab dosing regimens may indeed be optimized.

Pharmacokinetics

The PK of rituximab has been characterized in limited historical IV studies and more extensively in the SC development program. In the SC development program, a total of 8163 and 4739 quantifiable rituximab serum concentrations were available for PK characterization in NHL and CLL patients, respectively, following IV and SC dosing. The collected PK data enabled development of a population PK model that describes rituximab PK properties [6]. The structural model has been utilized for other anti-CD20 Mabs (e.g., obinutuzumab, ocrelizumab) reflecting its appropriateness and usefulness [7].

Rituximab PK is characterized by a two-compartment model with combined linear and time-varying clearance pathways. The linear clearance component reflects nonspecific endogenous catabolism and the specific time-varying clearance reflects a target-mediated process of rituximab binding to CD20 on B cells and their subsequent elimination, due to its mechanism of action. Indeed, following a short-term weekly treatment with rituximab IV 375 mg/m^2 for 4 weeks, Berinstein and colleagues observed a change in rituximab apparent half-life from the first to fourth dose and postulated that it was most likely related to the elimination of circulating CD20-positive B cells (i.e., target malignant B-cells), which serve to clear serum antibody with the initial infusions [8].

Population PK analysis of the extensive data collected in the SC development program estimated the rituximab time-varying clearance with a half-life of 9.3 days following eight cycles of every 3 week rituximab IV 375 mg/m^2 or SC 1400 mg dosing in NHL patients and 17.4 days following six cycles of every 4 week rituximab IV 500 mg/m2 or SC 1600 mg dosing in CLL patients [4, 5, 9]. The analyses indicate that the time-varying (target-mediated) clearance component becomes negligible with continued dosing to steady-state and thus suggests near-complete saturation and/or elimination of B cells over time with the approved regimens. Thus, these PK observations help confirm that the approved rituximab dosing regimens are appropriate to eliminate its target antigen in responding patients. In addition, they also support the use of C_{trough} as an appropriate measure of expected target saturation/elimination for PK bridging between routes [2].

The SC development program also supported that fixed rituximab SC doses resulted in systemic exposures (C_{trough} and AUC) that were non-inferior/higher than corresponding approved IV dosing regimens in NHL and CLL patients [2]. Those results suggest similar target saturation and expected clinical benefit. Additionally, whereas body size was a covariate on rituximab PK, the overall PK variability was not markedly different with flat vs BSA-based dosing, which supported the approval of flat dosing for rituximab SC dosing regimens.

Clinical efficacy and safety

Rituximab IV has been extensively studied in numerous large clinical trials (Table 1) [1]. Whether administered as a single agent or in combination with chemotherapy, rituximab IV has been shown to prolong progression-free survival (PFS), and in some indications overall survival (OS), across B-cell malignancies [1]. The clinical efficacy and safety profiles of rituximab were also investigated as part of the SC clinical development program in the NHL, DLBCL, and CLL populations using the approved IV and corresponding SC dosing regimens; in combination with chemotherapy [2]. Pharmacodynamics (i.e., B-cell depletion) and primary efficacy results demonstrated comparable outcomes for IV and SC routes confirming the PK-based clinical bridging approach for establishing the SC route [2]. Subgroup analyses showed similar benefit across groups including those with expected variations in PK between administration routes (e.g., BSA) suggesting rituximab benefit is consistent across the range of achieved exposures for the investigated dosing regimens (see also Exposure–response relationships below).

Exposure–response (ER) relationships

The evaluation of the relationship between rituximab exposure and clinical endpoints is limited, but supports evidence for ER relationships. Preclinical experiments have provided evidence of dose/exposure dependency on efficacy in mouse models [10]. Results from those experiments showed that the lowest tested dose did not modify survival, whereas

Table 1 Oncology randomized controlled trials that supported rituximab (IV) approvals

Indication	USPI study ID (#)[a]		Phase	n	n [b]	Population	Treatment	Rituxan dose	Primary efficacy results
	Study no.	Name							
iNHL	#4	M39021	III	322	–	Previously untreated indolent B-cell NHL	R-CVP	375 mg/m^2 q3w × 8	Median PFS 2.4 years for R-CVP vs 1.4 years for CVP (HR 0.44, 95% CI 0.29–0.65)
	#5	MO18264/PRIMA	III	1018	–	Previously untreated FL responding to R-chemo induction	Rituximab monotherapy	375 mg/m^2 q2m × 12	PFS was longer for R maintenance vs observation (HR 0.58, 95% CI 0.42–0.70)
	#6	ECOG E1496	III	311	–	Previously untreated, low-grade B-cell NHL responding to CVP chemotherapy	Rituximab monotherapy	375 mg/m^2 (q1w × 4) every 6 months × 4	Reduction in risk of progression, relapse or death in pts receiving R maintenance vs no intervention (HRs 0.36–0.49)
DLBCL	#7	ECOG E4494	III	632	–	Previously untreated DLBCL	R-CHOP	375 mg/m^2 (4–5 doses)	Median PFS 3.1 years for R-CHOP vs 1.6 years for CHOP (HR 0.69)
	#8	BO16368/LNH-98.5	III	399	–	Previously untreated DLBCL	R-CHOP	375 mg/m^2 q3w × 8	Median EFS 2.9 years for R-CHOP vs 1.1 years for CHOP (HR 0.60)
	#9	M39045/MInT	III	823	–	Previously untreated DLBCL	R-CHOP (or R-CHOP-like)	375 mg/m^2 q3w × 6	Median time to treatment failure was not reliably estimable for either pt group
Faster infusion rate (NHL)	#10	U4391g/RATE	III	363	14	Previously untreated FL or DLBCL	R-CVP or R-CHOP	375 mg/m^2 q3w × 6 or 8	Incidence of Grade 3–4 infusion reactions at Cycle 2 was 3.5% for R-CVP vs 0.0% for R-CHOP
CLL	#11	ML17102/CLL8	III	817	–	Previously untreated CLL	R-FC	C1: 375 mg/m^2 C2-6: 500 mg/m^2 q4w	Median PFS 39.8 months for R-FC vs 31.5 months for FC (HR 0.56, 95% CI 0.43–0.71, $p<0.01$)
	#12	BO17072/REACH	III	552	21	Previously treated CLL	R-FC	C1: 375 mg/m^2 C2-6: 500 mg/m^2 q4w	Median PFS 26.7 months for R-FC vs 21.7 months for FC (HR 0.76, 95% CI 0.6–0.96, $p<0.02$)

CHOP cyclophosphamide, doxorubicin, vincristine, prednisone, *CI* confidence interval, *CLL* chronic lymphocytic leukemia, *CVP* cyclophosphamide, vincristine, prednisone, *DLBCL* diffuse large B-cell lymphoma, *EFS* event-free survival, *FC* fludarabine, cyclophosphamide, *FL* follicular lymphoma, *HR* hazard ratio, *NHL* non-Hodgkin lymphoma, *PFS* progression-free survival, *R* rituximab

[a] Studies 1–3 in the Rituxan USPI were single-arm studies; only randomized controlled trials (i.e., Studies 4–12) are listed here

[b] Number of patients with PK samples

mice treated with higher rituximab doses had a significantly longer survival than those of the control group with median survival times [10]. Similarly, clinical investigations have identified or suggested relationships between rituximab dose/exposure and clinical outcomes. A graphical representation of clinical data collected from Berinstein and colleagues following of single agent rituximab IV 375 mg/m^2 administered weekly x 4 suggests an association between rituximab exposure and B-cell depletion when comparing responders and non-responders (Fig. 1; [8]). These data provide some evidence for ER and suggest greater exposures over longer treatment durations may improve outcomes. Of note, poor responding patients are often associated with higher tumor burden/target cells contributing to more rapid clearance (and thus lower exposure), which can complicate the interpretability of the ER relationship. Nonetheless, the observations are consistent with other published data supporting rituximab ER relationships to clinical outcomes [11–17].

Extensive ER analyses were undertaken in the SC development program in the large number of NHL and CLL patients from two clinical studies, SABRINA ($n = 410$) and SAWYER ($n = 176$), and one of the most exhaustive investigations of ER relationships with the approved rituximab dosing regimens was done [2]. Patients received rituximab IV 375 mg/m^2 or SC 1400 mg every 3 weeks for 8 cycles (NHL) or rituximab IV 500 mg/m^2 or SC 1600 mg every 4 weeks for 6 cycles (CLL), in combination with chemotherapy. Results from those analyses showed similar response rates (CR, PR, SD, and PD) across the range of rituximab exposures in both populations [4, 5, 9]. Further, a multivariate Cox proportional hazards analysis investigated the ER relationship for PFS using various functional (continuous and categorical) forms of rituximab exposure in each study [3, 4]. The analyses comprehensively investigated the ER relationship while accounting for other potential influencing factors (e.g., baseline demographics, disease characteristics and severity, and drug-related factors such as the presence or absence of anti-rituximab antibodies) on PFS. In both populations, the administered rituximab dosing regimens in combination with chemotherapy showed no evidence for rituximab ER in the majority (≥ 94%) of patients. This further supports the hypothesis of near-complete target saturation/elimination for maximizing expected clinical benefit. The remaining minority of patients had the lowest rituximab exposures (< 34 μg/mL) and a significantly greater

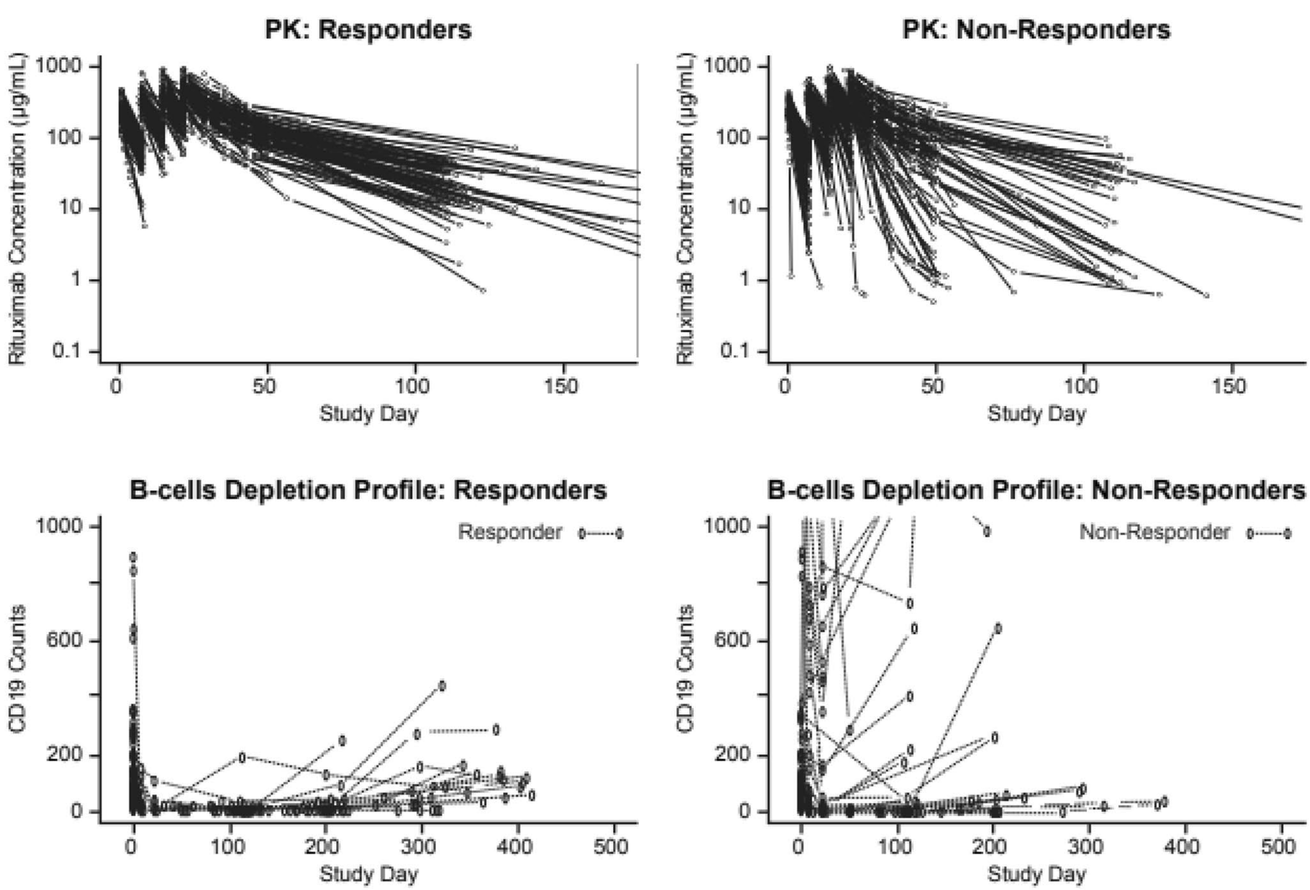

Fig. 1 Rituximab exposure and B cell depletion in responders and non-responders following weekly doses of rituximab 375 mg/m^2 for 4 weeks

risk of progression. Most of those patients also exhibited high tumor burden and/or target cells, which may also reflect worse overall disease burden, contributing to rapid progression and/or high rituximab clearance. The results of the ER analyses confirm the overall efficacy results from the SC development program. Namely, the consistent efficacy of rituximab IV and rituximab SC was demonstrated across primary and secondary endpoints as assessed by response rates and time-to-event endpoints (PFS, OS) [2, 4, 5]. Thus, ER analysis of data in NHL and CLL populations demonstrated that the majority of patients derived clinical benefit from rituximab independent of exposure and route of administration for the endpoints investigated and supports the overall consistency of the efficacy profiles via either route of administration [3, 4].

In terms of safety, comprehensive ER analyses investigated the relationship between rituximab exposure and key safety events including serious adverse events (SAEs), Grade ≥ 3 AEs, serious infections, administration-related reactions (ARRs), and changes in neutrophil counts. While some safety results differed in incidence between the two routes (namely local reactions, such as mild to moderate pain and swelling, were higher with SC administration, reflecting the expected change of the administration-related reaction profile), ER results demonstrated no relationship between investigated safety endpoints and rituximab exposure supporting its tolerability [9]. The extensive investigations also provided an opportunity to carefully examine the immunogenicity potential of rituximab following IV and SC dosing. Results from the NHL and CLL population showed low incidence of anti-rituximab antibodies following either route with no notable differences between routes [2, 4, 5].

Overall, the completed ER analyses from the SC development program in a large number of patients demonstrate that for approved rituximab IV or SC regimens in combination with chemotherapy, the observed benefit is maximized in the majority of patients.

Current perspective

The clinical benefit of rituximab is clear; however, although widely utilized over the past 20 years, questions about its approved dosing regimens are still often raised [1]. The recently completed SC development program, which collected extensive PK data, enabled reinvestigation of rituximab dose selection. ER analyses confirmed rituximab efficacy across the range of rituximab exposure in NHL and CLL patients. In the vast majority of the NHL and CLL patients included in the ER analyses, no relationship was identified between rituximab exposure and PFS using multivariate analyses which accounts for potential influencing factors. These analyses suggest that the approved IV and SC dosing regimens used in the SC development studies in combination with chemotherapy provide rituximab exposures within the plateau of efficacy and no further substantial clinical benefit may be expected with higher doses. Thus, these analyses provide a definitive assessment of PK and ER properties for rituximab in NHL and CLL patients and support the appropriateness of its approved dosing regimens for both routes of administration. These outcomes are also supported by recent semi-mechanistic PK/PD modeling of data collected from CLL patients in which simulated alternative dosing of rituximab confirmed lack of additional benefit [18]. ER analyses for safety events demonstrating no significant relationships to key safety events confirmed the overall tolerability profile of rituximab. Overall, based on the available clinical data and analyses, it is not expected that adjustments to the approved rituximab IV and SC dosing regimens (in combination with chemotherapy) would improve the clinical outcome for the majority of treated patients. It should be noted that this current analysis is limited to investigations conducted in patients with hematological malignancies. Rituximab is approved for other indications including rheumatoid arthritis (RA), granulomatosis with polyangiitis, microscopic polyangiitis, and pemphigus vulgaris which vary in terms of factors which may influence its PK or ER properties (e.g., lack of impact of tumor burden) [Rituxan USPI]. A review of clinical pharmacological data in those indications could further confirm the appropriateness of those approved dosing regimens.

Funding This work was supported by F. Hoffmann-La Roche.

Compliance with ethical standards

Conflict of interest P. N. Morcos and A. Boehnke are employees of, and own stock/stock options in, Roche. N Valente is an employee of Genentech and own stock/stock options in Roche.

Ethical approval All procedures performed in clinical studies with human subjects were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards and with the ethical standards of the institutional and/or national research committee.

Informed consent Informed consent was obtained from all human subjects included in the studies.

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