

REVIEW

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Rituximab and new regimens for indolent lymphoma: a brief update from 2012 ASCO Annual Meeting

Jiangning Zhao^{1†}, Zhenshu Xu^{2†}, Delong Liu^{3*} and Quanyi Lu^{1*}

Abstract

Indolent lymphoma (IL), the second most common lymphoma, remains incurable with chemotherapy alone. While R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) remains the standard frontline regimen for diffuse Large B-cell lymphoma, the optimal chemotherapy regimen for frontline therapy of advanced IL remains uncertain. FCR (fludarabine, cyclophosphamide, rituximab) has been shown to be better than fludarabine alone and fludarabine plus cyclophosphamide for IL. In FOLL05 trial, R-CHOP was compared with R-CVP (cyclophosphamide, vincristine, prednisone) and R-FM (fludarabine, mitoxantrone). The study showed that R-CHOP appears to have the best risk-benefit ratio for IL. The StiL NHL1 trial showed that BR (bendamustine, rituximab) has longer progression free survival and is better tolerated than R-CHOP. Long-term complications with secondary malignancies between the two regimens appear to be comparable. In this review, new combination regimens reported at 2012 ASCO annual meeting were evaluated for frontline and salvage therapy of indolent lymphoma.

Rituximab has essentially changed the natural history of diffuse Large B-cell lymphoma (DLBCL) [1-7]. R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) remains the standard frontline regimen for DLBCL [8-11]. New agents and biomarkers are being studied in an attempt to improve upon the current efficacy of R-CHOP [12-19]. Meanwhile, indolent lymphoma, the second most common subtype of lymphoma, remains incurable with chemotherapy alone [20-23]. FCR (fludarabine, cyclophosphamide, rituximab) has been shown to be better than fludarabine alone and fludarabine plus cyclophosphamide for untreated chronic lymphoid leukemia (CLL) [24-26]. Another regimen, PCR (pentostatin, cyclophosphamide, rituximab), was found to be comparable to FCR for untreated CLL [21]. In this review, new combination regimens reported at 2012 ASCO annual meeting were evaluated for frontline and salvage therapy of indolent lymphoma.

Rituximab for low burden indolent lymphoma

For low burden indolent lymphoma (LBIL), the standard approach is still “watch & wait”. A randomized study was conducted for low burden IL, the E4402 RESORT study [27]. The hypothesis was that rituximab (R) treatment of LBIL and maintenance rituximab (MR) would be superior to rituximab retreatment at disease progression. LBIL (small lymphocytic lymphoma, MZL, FL) were treated with R weekly x 4, then responders were randomized to receive MR (R x 1 q 3 months until progression), or RR (R weekly x 4 at progression). The primary endpoint was time to treatment failure (TTF). At the 2011 ASH meeting update, 384 with FL were enrolled. Overall response (CR + PR) was 71%. These 274 responders were then randomized to MR (n = 140) or RR (n = 134). The median follow-up was 3.8 yrs. There was no significant difference in TTF between the two groups (MR 3.9 yr vs. RR 3.6 yr). At 3 yrs, the rate of time to cytotoxic chemotherapy (TTTC) was 95% for MR vs. 86% for RR patients (p = .027). Therefore, MR and RR were comparable for the primary endpoint, TTF.

The E4402 results on non-FL lymphomas (SLL, MZL) were presented at 2012 ASCO [28]. A total of 137 non-FL patients were enrolled. Overall response (CR + PR) was 41% (n = 57). These 57 patients were then

* Correspondence: DELONG_LIU@NYMC.EDU; quanyilu@hotmail.com

[†]Equal contributors

³Division of Hematology and Oncology, New York Medical College and Westchester Medical Center, Valhalla, NY 10595, USA

¹Department of Hematology, Zhongshan Hospital of Xiamen University, Xiamen 361004, China

Full list of author information is available at the end of the article

randomized to MR (n = 32) or RR (n = 25). The median follow-up was 4.3 yrs. TTF of MR group was better than that of RR group (MR 3.74 yr vs. RR 1.07 yr, $p = 0.0002$; HR 4.95). At 3 yrs, the rate of freedom from cytotoxic treatment was 100% for MR vs. 70% for RR patients ($p = 0.0002$). There were 2 patients with grade III-IV toxicity (1 neutropenia, 1 encephalopathy) in MR group. In conclusion, this planned subgroup analysis for non-FL patients revealed significant benefits in TTF and TTTC.

These results in non-FL differ from those of FL patients in this trial. The overall response rate to R induction was higher in FL patients (FL 71% vs. non-FL 41%; $p < .0001$), but no TTF benefit was observed with MR for FL patients.

Rituximab: study of pharmacokinetics (PK) and pharmacodynamics (PD) for faster infusion

Rituximab (R) is typically infused over 4–6 hours. Faster infusion can improve patient's convenience and optimize utilization of oncology unit resources. A prospective, open-label, multicenter, single-arm trial was conducted to assess the safety, PK and PD of a 90-min infusion rate for R in NHL patients [29]. Patients (≥ 18 yrs old) with untreated DLBCL or FL received R-chemotherapy at the standard infusion rate (4–6 h) in cycle 1. Further R infusion was given over 90-min to patients who had no severe reactions and had circulating lymphocyte counts $\leq 5000/\mu\text{l}$ prior to cycle 2. A total of 14 patients who completed all cycles with faster infusion were asked to provide further serum samples up to 16 weeks after the last chemotherapy cycle. PK parameters, including R terminal half-life ($t_{1/2}$), maximum serum concentration (C_{max}), systemic clearance (CL) and volume of distribution (V) were evaluated. A total of 365 patients received the 90-min infusion rate at cycle 2. Peak R levels were higher than seen in published data of q3w R regimens but comparable with levels seen for q1w R regimens. The PK data and B cell (CD19+) depletion were similar between the groups of faster infusion and standard rate. These results suggest that a faster infusion of R has similar safety and PK data to the standard infusion rate. It is however important to evaluate the efficacy and the long-term outcome of the lymphoma treated at the faster infusion rate.

R-CVP vs R-CHOP vs R-FM: the final analysis of FOLL05 trial

There has been no international consensus on frontline optimal chemotherapy regimen for patients with advanced follicular lymphoma (FL). A final report of FOLL05 trial was presented at 2012 ASCO on a randomized comparison of R-CVP x 8 vs R-CHOP x 6 vs R-FM x 6 [30]. Maintenance therapy was not allowed in this randomized trial. The primary end point was time

to treatment failure (TTF) which was defined as failure of induction therapy, progressive or relapse disease and death from any causes. A total of 534 patients were enrolled; 30 were not evaluable. The patients' characteristics were as the following: median age = 56 years (range 30–75), 63% of patients had stage IV disease, 37% had unfavorable disease (FLIPI score 3–5).

There was no significant difference of overall response rate (CR + PR) for the whole group (91%, $p = 0.247$). The median follow-up time was 34 months. The 3-year TTF for patients treated with R-CVP, R-CHOP and R-FM was 46%, 64% and 61%, respectively (R-CHOP vs R-CVP $p = 0.007$; R-FM vs R-CVP $p = 0.021$; R-FM vs R-CHOP $p = 0.969$). Therefore, R-CVP had the worst TTF among the three groups.

The 3-year overall survival rate (OS) was not significantly different among the three groups (R-CVP 98%, R-CHOP 95%, and R-FM group 93%). Patients in R-FM group had a higher rate of severe neutropenia (64% vs 28% R-CVP, $p < 0.001$; vs 50% R-CHOP, $p = 0.015$).

At this final analysis, a total of 23 patients developed secondary malignancies (R-CVP 2%, R-CHOP 3% and R-FM 8%), indicating a higher incidence of secondary malignancies in R-FM group.

In summary, R-CHOP appears to be the best among the three with regard to the risk-benefit consideration for frontline therapy of advanced follicular lymphoma. One weakness of the trial was that it used CT instead of more sensitive PET scan to define complete response. In addition, TTF could have been improved if maintenance therapy was included [3,31].

BR vs R-CHOP: StiL NHL1 trial update

Bendamustine has been used for frontline treatment of CLL and for relapsed /refractory indolent lymphoma [32–36]. However its role in frontline therapy of indolent lymphoma has not been established. BR was compared with R-CHOP in a multicenter, randomized, phase III study for first-line treatment, the StiL NHL1 trial [37]. Patients with newly diagnosed indolent lymphoma and mantle cell lymphoma were enrolled. An updated analysis with a cut-off date for 31 Oct 2011 was presented at 2012 ASCO. The primary endpoint was PFS. Patients received a maximum of 6 cycles after randomization. The study enrolled 549 patients, 514 of them were evaluable (261 BR; 253 R-CHOP). The median age was 64 years.

The median follow-up was 45 months at this update. The PFS of BR was more than doubled in comparison with that of R-CHOP (69.5 versus 31.2 months; HR 0.58, 95% CI 0.44–0.74; $p < 0.001$). This advantage of BR was seen across all histological subtypes except marginal zone lymphoma. This advantage of BR was true both for

patients ≤ 60 years ($n = 199$, HR 0.52, $P = 0.002$), and for patients > 60 years ($n = 315$, HR 0.62, $P = 0.002$).

This update also reported more results based on risk factors. Compared with R-CHOP, BR significantly prolonged PFS in patients with normal LDH ($P < 0.001$). The longer PFS with BR was seen in both favorable (0–2 factors, $p = 0.043$) and unfavorable (3–5 factors, $p = 0.068$) FLIPI subgroups of patients with follicular lymphoma.

There were 74 treatment failures in the BR group, 116 in the R-CHOP group. In the R-CHOP group, 45% (52/116) received BR as salvage regimen. There was no significant difference in overall survival. Previously there have been unanswered questions regarding long-term complications with bendamustine. At this update, more information was provided in terms of secondary malignancies. With a median follow-up of 45 months, there appears to have no significant differences for secondary malignancies between the two groups (20 in BR, 23 in R-CHOP). In particular, there was one hematological malignancy in each group (1 MDS in BR, 1 AML in R-CHOP).

With this updated analysis, it appears that for newly diagnosed indolent lymphoma and elderly patients with MCL, BR has longer PFS and is better tolerated than R-CHOP. Long-term complications with secondary malignancies appear to be comparable.

R-CHOP vs CHOP-I¹³¹ tositumomab

Two agents have been approved for lymphoma radioimmunotherapy [38–45]. SWOG and CALGB intergroup trial, S0016, enrolled 554 patients between 3/1/2001 and 9/15/2008 to compare the safety and efficacy of 2 immunochemotherapy regimens, R-CHOP vs CHOP-I¹³¹ tositumomab (CHOP-RIT), for untreated patients with bulky stage II, III or IV FL [46]. Patients were randomized to CHOP-R x 6 or CHOP-RIT X 6. Both treatment regimens had excellent outcome with no significant differences (2 yr PFS: CHOP-R 76% vs CHOP-RIT 80%, $p = 0.11$; 2 yr OS: CHOP-R 97% vs CHOP-RIT 93%, $p = 0.08$). The serum $\beta 2M$, LDH level, and FLIPI score were found to be the strongest prognostic factors for PFS and OS by multivariable analysis.

Gemcitabine, rituximab and oxaliplatin (GROC)

Oxaliplatin has been studied for lymphoma therapy in various combination regimens [47–50]. Recently, in the salvage setting for relapsed/refractory NHL, gemcitabine, rituximab and oxaliplatin (GROC) was shown in a phase II trial to have an overall response rate of 58%, grade 3–4 thrombocytopenia of 9% and neutropenic fever of 3.5% [51]. No severe non-hematologic toxicities were observed. Patients received rituximab (375 mg/m^2) on day 1. On day 2, patients received gemcitabine (1000 mg/m^2) and oxaliplatin (100 mg/m^2). This was repeated every two weeks. A total of 58 patients were enrolled. The median age was

72 years (range 24 to 88 years). Median PFS was 134 days (95% CI 115–153) and median OS was 296 days (95% CI 164–428). The risk factors of age, IPI, LDH and albumin level did not influence the responses, but prior rituximab ($p = 0.02$) and response to initial therapy ($p = 0.04$) correlated with better outcomes. Therefore, GROC may be a useful salvage regimen for relapsed/refractory NHL. After complete of GROC therapy, 9 patients were successfully mobilized, collected and transplanted.

Conclusions and future directions

The optimal chemotherapy regimen for frontline therapy of advanced indolent lymphoma remains uncertain. Compared with R-CVP and R-FM, R-CHOP appears to have the best risk-benefit ratio. The StiL NHL1 trial showed that BR has longer PFS and is better tolerated than R-CHOP. Long-term complications with secondary malignancies between the two regimens appear to be comparable. Many novel agents with different mechanisms of action are being explored [52–55]. The Bruton's tyrosine kinase inhibitors appear to be very active in chronic lymphoid leukemia and refractory lymphoma [56–59]. It would be interesting to see whether adding novel agents to BR or R-CHOP can further improve the outcomes of advanced indolent lymphoma.

Abbreviations

CR: Complete response; CRu: Complete response unconfirmed; PD: Pharmacodynamics; PK: Pharmacokinetics; PR: Partial response; ORR: Overall response rate; OS: Overall survival; PFS: Progression free survival; SD: Stable disease; TTF: Time to treatment failure; CLL: Chronic lymphoid leukemia; DLBCL: Diffuse Large B-cell lymphoma; FL: Follicular lymphoma; IL: Indolent lymphoma; MCL: Mantle cell lymphoma; MZL: Marginal zone lymphoma; SLL: Small lymphocytic lymphoma; FCR: Fludarabine, cyclophosphamide, rituximab; PCR: Pentostatin, cyclophosphamide, rituximab; R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP: Cyclophosphamide, vincristine, prednisone; R-FM: Fludarabine, mitoxantrone.

Competing interests

Authors have no relevant conflict of interest.

Authors' contribution

DL and QL designed the study. All authors participated in data collection and draft preparation. All authors read and approved the final manuscript.

Author details

¹Department of Hematology, Zhongshan Hospital of Xiamen University, Xiamen 361004, China. ²Institute of Hematology, Fujian Union Hospital, Fuzhou, China. ³Division of Hematology and Oncology, New York Medical College and Westchester Medical Center, Valhalla, NY 10595, USA.

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