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A Canadian perspective by:

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A CANADIAN PERSPECTIVE

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Overview

The International Conference on Malignant Lymphoma (ICML) is held every three years in Lugano, Switzerland. ICML started nearly 25 years ago as a small expert workshop. It has since grown to be one of the leading congresses in this therapeutic area with the attendance in 2005 reaching almost 3000 delegates.

At the 9th annual conference held from June 8 to 11, 2005, international experts in the field of lymphoma research and treatment met to discuss the current status and recent research results regarding lymphoma treatment. One event drawing considerable attention was the controversy session debating rituximab use in the treatment of patients with diffuse large cell lymphoma.

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Summary of Controversy II: "Is R-CHOP the standard treatment for DLCL?"

During the 2005 ICML controversy session "Is R-CHOP the standard treatment for DLCL?" speakers Dr. Richard I. Fisher from the University of Rochester in New York and Dr. Michael G. Pfreundschuh from the University of Saarland in Homburg, Germany discussed the pros and cons of adding rituximab to conventional chemotherapy when treating diffuse large cell lymphoma (DLCL) patients.

First, Dr. Fisher presented data in favour of R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) treatment. Dr. Pfreundschuh followed with evidence demonstrating that the benefit of R-CHOP has been proven in only approximately 10% of lymphoma patients.

Fisher referred to three major studies supporting the use of R-CHOP:

- The **MInT** (Mabthera International Trial Group) study[1] examined the effects of adding rituximab to conventional chemotherapy in adult patients younger than 60 years of age with low-risk DLCL. After a preliminary analysis at 22 months, the trial was stopped due to the favourable results for rituximab. As in the German NHL-B1 study,[2] the CHOEP-21 (CHOP plus etoposide) control arm of the MInT study was superior to the CHOP-21 control arm (2-years time to failure (TTF): 65% vs. 55%).[3] The addition of rituximab to these regimens increased the efficacy significantly, but there was no difference between R-CHOP-21 and R-CHOEP-21 (2-years TTF: 83% vs. 80%).

- The **US Intergroup** (CALGB 9793/ECOG-SWOG 4494)[4] study showed a benefit of combining rituximab with CHOP as either induction or maintenance therapy, but not both. The average relative dose intensity (ARDI) of CHOP and R-CHOP, specifically of cyclophosphamide and adriamycin, can be maintained in a majority of previously untreated DLCL patients > 60 years of age. The addition of rituximab to the CHOP regimen does not impact the ARDI. A decreased RDI of CHOP therapy was seen in patients with advanced age (> 75 years of age), limited stage disease and baseline hemoglobin (<120 g/L).[5]

- The **GELA** (Groupe d'Etude des Lymphomes de l'Adulte) study[6] demonstrated significantly improved outcome in elderly patients receiving R-CHOP-21 compared to CHOP-21. A comparable improvement in outcome was achieved with a dose-dense CHOP-14 regimen.[7] Fisher concluded that R-CHOP-21 is less toxic than CHOP-14 and therefore the new standard regimen. However, there remains an excess of mortality (2%) when compared with the general population.[8]

Despite the strong evidence as presented by Fisher, Pfreundschuh reminded the audience that the benefit of rituximab is clearly proven by clinical trials in only 10% of patients and he warned of extrapolating these results to all patients with DLCL.

In his presentation, Pfreundschuh delivered the evidence as it applies to three patient subpopulations according to the classification used by the German NHL study group:[2] young patients (≤ 60 years), good prognosis (aaIPI < 2); young patients, bad prognosis; and elderly patients.

Young patients, good prognosis (~22% of DLCL patients)

The addition of rituximab to CHOP-like regimen significantly improved overall results in young patients with good prognosis.[1] However, a subgroup analysis of the ECOG 4494 study showed that only patients without BCL-6 protein expression (BCL-6 negative) profit from rituximab.[9] Approximately 50% of patients are BCL-6 negative. Therefore, Pfreundschuh summarized, only 10% of young DLCL patients with good prognosis and without BCL-6 protein expression clearly profit from rituximab.

Young patients, poor prognosis (~18 % of DLCL patients)

There are no data available from randomized trials that investigated the effect of rituximab in this patient group. A historical comparison by Wilson et al. and results from the German Mega-CHOEP phase 2 studies suggest that there may be no benefit at all for the addition of rituximab to intensive chemotherapy. In the ongoing Mega-CHOEP study the randomization in the control arm (CHOEP-14 ± rituximab) was stopped because of the results of the MInT study. Thus, the effect of rituximab in young patients with poor prognosis remains uncertain.

Elderly patients (~60% of DLCL patients)

Pfreundschuh also reported the results of the GELA study whereby R-CHOP improved outcome in elderly patients,[5,6,7] however, he concluded that the benefit of dose-dense CHOP-14 was achieved without added toxicity, offering an advantage in terms of patient convenience, shorter treatment duration (12 weeks vs. 24 weeks), and lower costs (approximately 10.000 vs. 30.000 per patient). Furthermore, the first planned interim analysis of an ongoing randomized trial (RICOVER-60, Pfreundschuh et al.) comparing six vs. eight cycles of CHOP-14 ± rituximab showed no further benefit for adding rituximab to CHOP-14. Thus, rituximab cannot be regarded as standard in elderly DLCL patients.

Table 1: Comparison of efficacy and safety results

	NHL-B2		GELA study	
	6x CHOP-14	6x CHOP-21	8x R-CHOP-21	8x CHOP-21
Patient number	172	178	197	202
5-years event-free survival[x,xx]	44 %	33 %	47 %	29 %
5-years overall survival [x,xx]	53 %	41 %	58 %	45 %
Adverse Events[y,x]				
Therapeutic deaths	2.9 %	3.4 %	6 %	6 %
Leukopenia	70 %	72 %	n/a	n/a
Infections	11 %	8.0 %	12 %	20 %
Cardiotoxicity	4.7 %	3.4 %	8 %	8 %

Conclusion

Pfreundschuh concluded the ICML controversy session by saying that rituximab is not the new treatment standard for all patients with DLCL. While the majority of audience members uses rituximab in DLCL patients, 50% of the participants admitted that they will reconsider their treatment behavior based on the evidence presented during the session. It is expected that further evidence, in particular from the US Intergroup trial will be presented at the American Society of Hematology annual meeting in December 2005.

References: 1. Pfreundschuh M, Trumper L, Gill D, et al. First analysis of the completed MInT trial in young patients with low-risk diffuse large B-cell lymphoma (DLBCL): addition of rituximab to a CHOP-like regimen significantly improves outcome of all patients with the identification of a very favorable subgroup with IPI=O and no bulky disease. *Blood.* 2004;104:48a Abstract #157. **2.** Pfreundschuh M, Trumper L, Kloess M, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: results of the NHL-B1 trial of the DSHNHL. *Blood.* 2004;104:626-633. **3.** Pfreundschuh M, Nickenig N, Kannourakis G, et al. Rituximab as a "chemo-equalizer" in the MInT (Mabthera International Trial Group) study: Treatment results of CHOP-21, CHOEP-21, MACOP-b and PMitCEBO with and without rituximab in young good-prognosis patients with aggressive lymphomas. ICML. 2005; Abstract # 208. **4.** Habermann TM, Weller E, Morrison VA, et al. Rituximab-CHOP versus CHOP with or without maintenance rituximab in patients 60 years of age or older with diffuse large B-cell lymphoma (DLBCL): An update. *Blood.* 2004;104:40a. Abstract #127. **5.** Morrison VA, et al.. Dose intensity of CHOP alone or with rituximab in diffuse large bcell lymphoma (DLBCL) in patients >60 years of age: An analysis of the Intergroup trial (CALGB 9793 ECOG-SWOG 4494). ICML. 2005;Abstract #224. **6.** Coiffier B, Lepage E, Brière J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med.* 2002;346:235–42. **7.** Pfreundschuh M, Trumper L, Kloess M, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL. *Blood.* 2004;104: 634–641. **8.** Mounier N , Henry-Amar M, Gisselbrecht C, et al. Is it possible to cure elderly patients with diffuse large B-cell lymphoma? A relative survival analysis of the R-CHOP study (GELA-LNH985) with long-term results. ICML. 2005; Abstract #227. **9.** Winter JN, Weller E, Horning SJ, et al. Rituximab (R) added to CHOP improves outcomes in BCL-6 negative but not in BCL-6 positive DLBCL patients > 60 years. ICML. 2005; Abstract # 209.

Dr. Bence-Bruckler's perspective:

Can you please provide the brief commentary on the following:

- Comment on your reaction and/or the group's reaction to the evidence presented during the session
- A brief outline the implications of this evidence
- Your anticipation of ASH 2005 to provide further evidence and outcomes

Adding Rituximab to the Treatment of Follicular Lymphoma

Posters presented by Imrie et al. and Hensel et al. provided promising evidence that adding rituximab to the standard chemotherapy treatment of follicular non-Hodgkin's lymphoma (NHL) may significantly improve response rates.

Imrie et al. previously published that the addition of rituximab to CVP chemotherapy (cyclophosphamide, vincristine, and prednisone) improved response rate and time to progression (TTP).[1] In their analysis according to baseline prognostic variables at 30-months median follow-up, they concluded that the addition of rituximab to first-line treatment with CVP improves response rate, response duration, and TTP without increasing toxicity. The TTP benefit of adding rituximab was observed in all prognostic groups. In the R-CVP treatment arm, only the FLIPI score offered additional predictive value.[2]

The multicentre, randomized phase II trial conducted by Hensel et al. addressed for the first time the optimal dosage of rituximab in combined immuno-chemotherapy. At the conference they presented the first interim analysis of how often rituximab should be added to standard chemotherapy to achieve maximum remission rates. They observed patients with untreated stage III/IV CD20 positive follicular NHL receiving six courses of standard CHOP-21 chemotherapy (cyclophosphamide, doxorubicine, vincristine, and prednisone) and who were randomly assigned to obtain rituximab (375 mg/m^2) at day 0 with the first CHOP course only, with the first three CHOP courses, or with all six CHOP courses. The group observed similar hematologic, gastrointestinal, and infectious toxicity in all treatment arms. High response rates were achieved in all treatment arms, with a trend towards better results in the 6xRituxi-arm. Further study is required and recruitment is ongoing. [3]

References: 1. Imrie K, Belch A, Pettengell R, et al. Rituximab plus CVP chemotherapy vs. CVP alone as first-line treatment for follicular lymphoma: Treatment effect according to baseline prognostic factors. ASCO. 2005; Abstract #6525. **2.** Imrie K, Belch A, Pettengell R, et al. CVP Plus Rituximab Compared to CVP Alone in Previously Untreated Patients with Follicular Lymphoma: Impact of Baseline Prognostic Factors. ICML. 2005; Abstract # 249. **3.** Hensel M, Scheuer L, Salwender H, et al. How much rituximab is needed for patients with follicular non-Hodgkin s lymphoma: A multicenter, randomized trial comparing 1, 3 or 6 infusions of rituximab added to 6 cycles of CHOP chemotherapy (HD2000-Trial). ICML. 2005; Abstract # 251.

Dr. Bence-Bruckler's perspective:

Can you please comment on the anticipation of further study results?

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