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Subanalysis of the StiL NHL 1-2003 Study:

Achievement of Complete Response with Bendamustine-Rituximab (B-R) and CHOP-R in the First-Line Treatment of Indolent and Mantle Cell Lymphomas Results in Superior Survival Compared to Partial Response

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Background:

An important question in the management of patients with indolent lymphomas surrounds the depth of response and whether the achievement of a high-quality response is associated with an improved outcome. The demonstration of such an effect may have implications for the choice of treatment, particularly for newly diagnosed disease. In addition, the finding of a prognostic impact may also aid the discussion of suitable endpoints in clinical trials (1).

There are some data to suggest that the achievement of a complete response is of prognostic importance in the treatment of front-line follicular lymphoma (FL) (2, 3). However, only limited information regarding the impact of achieving a high quality response on overall survival (OS) in the rituximab era are available.

The NHL 1 study, a prospective, multicenter, randomized, phase 3 study which compared B-R and CHOP-R as first-line treatment in indolent lymphomas and mantle cell lymphoma (MCL), demonstrated a significant benefit in progression-free survival (PFS) as well as improved tolerability for B-R compared with CHOP-R (4). Here we present an analysis of the impact of response quality on PFS and OS.

Methods:

514 patients with indolent or MCL were randomized to receive B-R or CHOP-R for a maximum of 6 cycles. Patient characteristics are listed in Table 1.

Results:

The overall response rate in the 514 patients (261 B-R; 253 CHOP-R) was 92.7% and 91.3% in the B-R and CHOP-R arms, respectively (4). A complete response (CR) was observed in 39.8% in the B-R arm and in 30% in the CHOP-R arm (p=0.021). The achievement of CR was associated with a significantly prolonged PFS and OS (Fig. 1 & 2, Table 2). Analysis by treatment arm revealed a trend for superior PFS and a significantly improved OS for patients achieving CR following treatment with B-R. In the CHOP-R arm, patients in CR had a significantly superior PFS compared to those in PR with a trend to superior OS.

Regardless of the quality of response, PFS was superior with B-R versus CHOP-R: For patients in CR, the median PFS was not reached with B-R, whereas for CHOP-R it was 53.7 months (p=0.0204; Fig 3). In patients achieving PR, treatment with B-R resulted in a median PFS of 57.2 months, and this was 30.9 months with CHOP-R (p=0.0002; Fig 4).

We noted a statistically significant difference in CR rates between male (n=272, median age 63 years) and female (n=242, median age 64 years) patients. The CR rate was 28.6% in male patients and 42.1% in female patients (p=0.0016). Female patients had a longer median PFS (51.4 months) compared to male patients (38.6 months) (Fig. 5), however, this difference was not statistically significant (p=0.0866).

Discussion:

The finding of prolonged PFS and OS following the achievement of CR versus PR may have implications regarding treatment strategies, particularly in the front-line setting. However, whether patients who do not achieve a PR should undergo further treatment with the goal of reaching a CR requires further investigation (2).

The superior CR rates seen for female versus male patients in our trial corroborate the results of a recently reported study of immunochemotherapy consisting of rituximab, fludarabine and mitoxantrone followed by rituximab maintenance in patients with newly diagnosed FL and may add further support to the proposal of a differentiated dosing schedule based on gender (5).

The availability of effective therapies has resulted in a long median survival for patients with lymphoma and as a consequence, there are ongoing discussions regarding suitable endpoints in trials (1). The demonstration of a prognostic impact of depth of response using conventional response assessment or methods, such as positron emission tomography-computed tomography (PET-CT) (6), are supporting the use of response quality as a surrogate marker for PFS or OS in trials.

Conclusion:

Patients in CR following first-line treatment had a significantly longer PFS and OS compared to those achieving a PR. Therefore, our results strongly suggest an association between quality of response and outcome, indicating that the achievement of a deep response should be an important goal in FL.

Table 1 Patient Characteristics

	B-R (n=261)	CHOP-R (n=253)
Age		
Median (range) — years	64 (34–83)	63 (31–82)
< 60 years — (%)	36·0	35·6
61–70 years — (%)	41·0	41·5
> 70 years — (%)	23·0	22·9
Stage (%)		
II	3·4	3·6
III	19·2	18·7
IV	77·4	77·8
Histology (%)		
Follicular	53·3	55·3
Mantle cell	17·6	18·9
Marginal zone	14·2	11·9
Lymphoplasmacytic	8·4	7·5
Small lymphocytic	3·8	4·3
Low grade, unclassifiable	2·7	1·9
B-symptoms (%)	38·3	29·2
Bone marrow involved (%)	67·8	67·2
Extranodal involved sites ≥1 (%)	81·2	76·3
LDH >240 U/L(%)	38·3	33·2
Median beta-2-microglobulin (mg/L)	2·6 (0·7–17·8)	2·4 (1·1–23·2)
Prognostic groups for all patients (IPI) (%)		
>2 risk factors	36·8	35·2
Prognostic groups for follicular (FLIPI) (%)		
Low risk (0–1 risk factor)	11·5	18·6
Intermediate risk (2 risk factors)	41·0	31·4
Poor risk (3–5 risk factors)	45·3	45·7

Fig. 1: PFS: CR vs PR, all patients

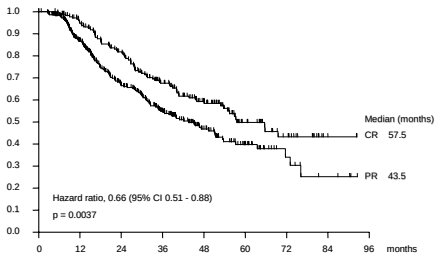


Fig 2: Overall survival: CR vs PR, all patients

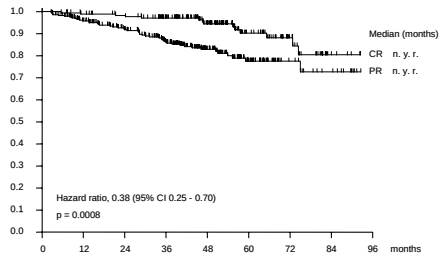


Fig. 3: PFS: BR vs CHOP-R, in patients with CR

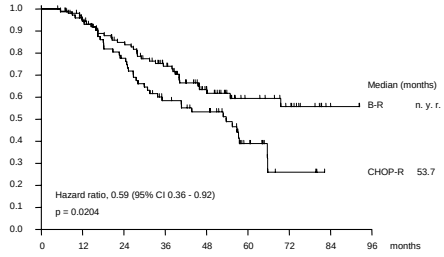


Fig. 4: PFS: BR vs CHOP-R, in patients with PR

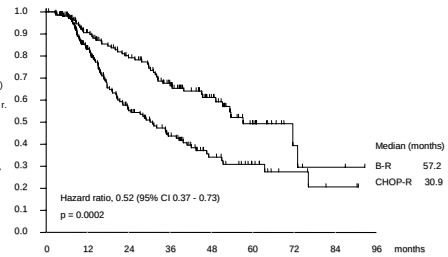
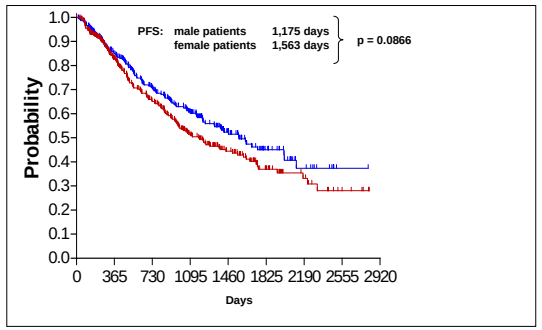


Table 2: PFS and OS according to quality of response

		CR	PR	p
All patients	**PFS (median)**	**57.5 months**	**43.5 months**	**0.0037**
	OS rate at 5 years	**90.3 %**	**77.5 %**	**0.0008**
B-R arm	**PFS (median)**	**not reached**	**57.2 months**	**0.1912**
	OS rate at 5 years	**91.0 %**	**80.1 %**	**0.0044**
CHOP-R arm	**PFS (median)**	**53.7 months**	**30.9 months**	**0.0215**
	OS rate at 5 years	**89.6 %**	**75.4 %**	**0.0737**

Fig. 5: PFS: BR vs CHOP-R, in male (red) and female (blue) patients



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