Session 13: indolent lymphoma

134 INTERNATIONAL PHASE III STUDY OF CHLORAMBUCIL VERSUS FLUDARABINE AS INITIAL THERAPY FOR WALDENSTRÖM'S MACROGLOBULINEMIA AND RELATED DISORDERS: RESULTS IN 414 PATIENTS ON BEHALF OF FCGCLL/WM, GOELAMS, GELA AND NCRI

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Waldenström's macroglobulinemia (WM) and related-disorders (Marginal Zone Lymphoma: MZL, and non immunoglobulin IgM lymphoplasmacytic lymphoma: LPL) are rare diseases. Very few randomized trials were reported in this setting. Most commonly patients with WM are initially treated with an alkylating agent, such as chlorambucil (CBL) or with a nucleoside analogue such as fludarabine (F) or 2CdA, alone or in association. The WM1 study was a prospective international randomized open-label study that included patients with previously untreated WM MZL and LPL. At registration, patients were stratified as having WM, SLVL, or LPL, and were randomized in the two arms. The aim of the study was to compare the efficacy of oral CBL at a dose of 8 mg/m2 for 10 days every 28 days to a maximum of 12 cycles with oral F at a dose of 40 mg/m2 orally for 5 days every 28 days to a maximum of 6 cycles. 418 patients were enrolled into the study from 07/01 to12/09. 414 patients received at least one course of chemotherapy. There were 340 WM, 33 MZL and 41 LPL with a median age of 68 years (40-89). 207 patients were randomized in the F arm and 207 patients in the CBL arm. At inclusion, the median of haemoglobin (g/l), platelets (Giga/l), albumin (g/l) and beta 2 microglobulin (mg/l) were 10, 218, 37.1 and 3.49 respectively. The overall response rate (CR+PR) was 54.4% in the F arm versus 43% in the CBL arm (p=0.03). With a median follow-up time of 33.7 months, the median of progression free survival time (PFS) and time to treatment failure (TTF) were statistically longer in the F arm: PFS 36.4m vs 27.1 m (p=0.01) and TTF 38.3m vs 19.5 m (p= 0.001). In WM group, factors influencing negatively PFS were CBL arm, albumin< 35g/l and Beta2 microglobulin>3mg/l. Main toxicity was haematological with 13.6% vs 3.5% of grade IV thrombocytopenia and 12% vs 7% of grade IV anemia in F and CBL arms respectively. F by oral route is a safe and effective ambulatory treatment in WM patients, even the elderly and more effective than CBL with a duration of response over 3 years

135 R-CVP VS R-CHOP VS R-FM FOR THE INITIAL TREATMENT OF PATIENTS WITH ADVANCED STAGE FOLLICULAR LYMPHOMA. PRELIMINARY RESULTS OF FOLL05 IIL TRIAL

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Introduction: Though there is a general agreement in using rituximab in patients with advanced follicular lymphoma (FL) needing therapy, the optimal chemotherapy regimen to be associated with, is still a matter of debate.

Materials and Methods: Between March 2006 and September 2010, 534 adult patients with previously untreated stage II-IV FL were enrolled in a multicenter, randomized trial aimed at comparing the efficacy of 8 doses of rituximab associated to 8 cycles of CVP, or 6 cycles of CHOP or FM (fludarabine 25mg/m^2 day 1-3, mitoxantrone 10mg/m^2 day 1). The principal end point of the study was Time to Treatment Failure (TTF).

Results: Out of the 534 patients, 30 were subsequently excluded due to unconfirmed histology (18 cases), synchronous cancer (3 cases), consent withdrawal (8 cases), HIV positivity (1 case). The median patient age was 56 years (range 30-75), 62% of patients had stage IV disease, and 37% a FLIPI score >2. At the end of induction treatment the overall response rate (CR+ PR) for the whole group was 89% (p=0.075). After a median follow-up of 25 months, the 3-year TTF was 47%, 57% and 60% for patients treated with R-CVP, R-CHOP and R-FM respectively (R-CHOP *vs* R-CVP p=0.026; R-FM *vs* R-CVP p=0.023; R-FM *vs* R-CHOP p=0.979). At this point of time progression free survival did not significantly differ between groups. The 3-year overall survival rate was 97%, 96% and 92% for R-CVP, R-CHOP and R-FM group, respectively. Toxicity was mainly hematological with grade 3-4 neutropenia occurring in the 56% of patients. Subjects treated with R-FM had a higher rate of neutropenia (OR=9.37 *vs* R-CVP, p<0.001; OR=1.96 *vs* R-CHOP, p=0.004).

Conclusions: This preliminary analysis showed that R-CVP was associated with an inferior 3-year TTF compared with R-FM and R-CHOP. In addition, R-CHOP had an anti-lymphoma activity similar to R-FM with a better toxicity profile, and may now be considered as a standard regimen for the treatment of patients with advanced FL needing systemic therapy.

136 RITUXIMAB (R) IN COMBINATION WITH INTERFERON-A2A (IFN) SHOWS BETTER RESPONSE THAN SINGLE R IN PATIENTS WITH FOLLICULAR OR OTHER CD20+ LOW-GRADE (INDOLENT) LYMPHOMA. A RANDOMIZED PHASE III STUDY FROM THE NORDIC LYMPHOMA GROUP

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Introduction/Purpose: The best treatment in indolent lymphoma is not established. The aim of this study was to evaluate the effect of adding IFN to first-line R monotherapy with extended dosing in patients (pts) with CD20+indolent lymphoma and to define pts with no need of chemotherapy.

Patients and Methods: Pts with symptomatic, advanced indolent lymphoma (previously untreated or at first relapse after a short course of chlorambucil only) were randomized to R (Mabthera®) 375 mg/m2 once-weekly for 4 consecutive weeks or R with 5 weeks IFN (Roferon-A®) as priming (cycle 1). Patients achieving either a complete response (CR), partial response (PR) or a minor response (MR) at ten weeks, were planned to receive a second cycle with four infusions of R alone or combined with IFN (cycle 2).

Results: In total, 313 patients were randomized. The clinical characteristics between the groups were well balanced. After pathology review, 3 pts in each arm did not fulfill inclusion criteria: 5 DLBCL/ transformed and one Hodgkin. Most patients were previously untreated, but 11 pts in R only and 14 in R+IFN had had a previous response to chlorambucil. After cycle 1, responses among all 313 randomized pts were: 8.6 % CR/CRu, 47.9 % PR and 22.4 % MR. In total, 16.9 % were considered resistant (SD/PD). Responses in pts qualifying for cycle 2 were CR/CRu in 41% and 22.4% with R+ IFN (n = 123) and R (n = 124), respectively (p< 0.01). Also pts with FLIPI 3-5 showed a higher response with R+IFN than with R (CR/Cru 38.0% vs. 23.1%). More patients in the combination arm improved their response from PR/MR in cycle 1 to CR after cycle 2. In November 2010 the median follow-up time for all pts was 49.3 months. Data on failure-free survival will also be presented.

Conclusion: This randomized phase III trial demonstrates that extended rituximab dosing is safe and effective in patients with low-grade lymphoma, and shows improved response rates if combined with IFN.

137 LENALIDOMIDE PLUS RITUXIMAB IS A HIGHLY EFFECTIVE AND WELL-TOLERATED BIOLOGIC THERAPY IN UNTREATED INDOLENT B CELL NON-HODGKINS LYMPHOMA

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Background: Traditional regimens for newly diagnosed patients (pts) with indolent non-Hodgkins lymphoma (NHL) combining genotoxic chemotherapy with immunotherapy have response rates approaching 90%, although toxicity is common. Lenalidomide has been shown to have single-agent activity in relapsed NHL, and rituximab is effective alone and in combination with chemotherapy in untreated patients. Recent studies suggest that lenalidomide may repair immune synapse dysfunction in follicular lymphoma (FL) (Ramsey A, Blood 2009) and augment the activity of rituximab. The aim of this phase II study is to evaluate the efficacy and safety of lenalidomide and rituximab in pts with untreated, advanced indolent NHL.

Methods: Pts with untreated indolent NHL received 20 mg/day of lenalidomide on days 1-21 and rituximab 375 mg/m^2 on day 1 of each 28 day cycle. Prophylactic growth factors were not used. Response was assessed every 3 cycles using 1999 International Working Group Criteria.

Results: 75 pts have completed 6 cycles of treatment or are off-study, and 70 pts are evaluable for response. Histologies included: CLL/SLL n=15, FL n=41, and marginal zone lymphoma n=19. The median age was 57 (35-84), and 55% were male. The overall response (OR) rate for all pts was 90% with 66% attaining a complete response (CR). Seventeen pts (25%) had a partial response, and stable disease was noted in 6 (9%). OR and CR rates were impressive in FL, with 34/39 (87%) evaluable patients attaining a CR. At study entry 80% of FL pts had a FLIPI score of ≥ 2 and 54% met GELF criteria for high tumor burden. Responses were high regardless of FLIPI or GELF criteria. Following cycle 6, nearly all FL patients demonstrated molecular response without detectable BCL-2 by PCR.At a median follow up of 14.4 (7-32.5) months, 4 pts experienced progression of disease. The most common grade ≥ 3 non-hematologic toxicities included rash (7 pts), muscle pain (7pts), thrombosis (3pts) and infection (3pts). Grade ≥3 neutropenia and thrombocytopenia occurred in 20 (27%) and 4 (5%) pts respectively. Five pts stopped treatment due to adverse events, all occurred during first two cycles, including 1 grade 3 rash, 1 arterial thrombosis, 2 infusion reactions and 1 transient episode of respiratory failure during cycle 1.

Conclusion: The biologic agents lenalidomide and rituximab as front line therapy produce excellent overall and complete response rates with manageable toxicity in pts with indolent B cell NHL. Randomized studies are planned utilizing this regimen in untreated FL.

138 HEMATOLOGICAL RESPONSE TO ANTIVIRAL TREATMENT IN 94 PATIENTS WITH INDOLENT B-CELL LYMPHOMAS ASSOCIATED WITH HEPATITIS C VIRUS INFECTION: A STUDY OF THE FONDAZIONE ITALIANA LINFOMI (FIL)

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Introduction: Hematological response after antiviral therapy (AT) is the strongest argument in favourof an oncogenic role of hepatitis C virus (HCV) in non-Hodgkin's B-cell lymphoma (NHL). A systematic review has shown that a complete remission (CR) is achieved in 75% of cases (Gisbert 2005); this evidence is based on 65 cases from 16 studies, mostly constitued by small series with insufficient follow-up; this inconsistent evidence hampers definitive conclusion on the anti-lymphoma role of AT and the long-term outcome of these pts.

Methods: We analysed virological and hematological response of 94 pts with indolent B-NHL and and HCV infection treated with AT (76 as first-line treatment and 18 as second-line after failure of conventional treatments). All pts were characterized by an indolent course of disease not needing immediate conventional anti-lymphoma therapy. 36 pts received interferon (IFN) (in 26 with ribavirin) and 57 received peg-IFN (in 53 plus ribavirin).

Results: Histological, virological and hematological features are summarized in Table 1. Six pts discontinued AT for toxicity or absence of virological response; no pt interrupted AT for NHL progression. Of pts treated with AT as first line, 36 (47%) achieved a CR and 23 (30%) a PR while 14 had stable disease; with a median F-UP of 3.3 yrs, median duration of response was 23 mo. A sustained virological response (SVR) was achieved in 59 pts (78%). Of pts treated with AT as second line, 5 (27%) achieved a CR and 9 (50%) a PR; a SVR was achieved in 10 pts (56%). With a median F-UP of 4.3 yrs, median duration of response was 26 mo.

Considering the group treated with AT as first line, hematologic response (CR + PR) was highly significantly associated to the achievement of a SVR (p <0.001) while NHL regression did not correlate with the histotype, the HCV genotype (1 vs. 2) and the type of AT (IFN-based vs peg-IFN-based). Elevatedb_2-microglobulin and albumin level < 3.5 g/dl were significantly associated with failure of hematological response (respectively p=0.02 and p=0.03). For pts treated with AT as first line 5-yr OS was 94%; 6 pts died (3 for NHL progression, 2 for HCC and 1 for infection). 5-yr PFS was 78%; PFS were significantly longer in pts who underwent peg-IFN-based AT (p=0.001).

Conclusions: These data in a large series of pts confirm high rates of lymphoma regression in pts with indolent NHL treated with AT. Despite similar rates of response between IFN and peg-IFN, peg-IFN-based AT seems able to guarantee a better long term control of lymphoma. Lower response rate in second line suggests AT as front-line approach in this setting if an immediate conventional immunochemotherapy program is not needed.

Table 1

	First-line AT (76)		Second-line AT (18)	
	N	%	N	%
Age, median (range)	62 (24 - 77)	-	55 (23 - 72)	-
M/F	35/41	46/54	9/9	50/50
- Marginal-zone lymphoma	47	62	10	55
Splenic	24	32	6	33
Nodal	6	8	1	6
Extranodal of MALT	17	22	3	16
- Follicular lymphoma	3	4	2	11
- Lymphoplasmacytic lymphoma	1	1	2	11
- Mantle cell lymphoma	0	0	1	6
- Small lymphocytic lymphoma	0	0	1	6
- Low-grade B-cell NHL NOS	25	33	2	11
Ann Arbor stage III-IV	70	92	13	72
Elevated b_2-microglobulin (n 50)	23	57	9	90
Albumin <3.5 g/dl	5	7	2	11
Serum MC	20	26	9	50
HCV genotype (n 78)				
- 1	26	41	8	57
- 2	35	53	4	29
- 3	2	4	2	14
- 5	1	2	0	0
Cryoglobulins (n 78)	20	32	9	60
Symptomatic cryoglobulinemia (n 78)	6	10	7	47