‘‘Focus on…’’ session: new drug combinations

109 ORAL LENALIDOMIDE PLUS 4 DOSES OF RITUXIMAB INDUCED PROLONGED REMISSIONS IN RELAPSED/REFRACTORY MANTLE CELL LYMPHOMA: A COMPLETED PHASE I/II CLINICAL TRIAL

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Background: Mantle cell lymphoma (MCL) is not yet curable and new agents are needed for relapsed and refractory disease. An oral immunomodulatory agent such as lenalidomide could be effective with minimal toxicities especially when combined with the anti-CD20 antibody rituximab.

Purpose: To determine the maximum tolerated dose (MTD) in phase I; and to evaluate the efficacy and safety of lenalidomide plus rituximab in phase II for patients with relapsed/refractory MCL.

Patients and Methods: Patients received oral lenalidomide (range 10–25 mg) on days 1–21 of every 28-day cycle, and intravenous rituximab weekly for 4 doses during cycle 1. Treatment continued until disease progression or severe toxicity.

Results: A total of fifty-two (52) patients were enrolled, including 14 in phase I and 46 in phase II (8 from phase I). Median number of prior therapies for all 52 patients was two (range 1–4). The MTD was oral lenalidomide 20 mg daily, 21 days on and 7 days off plus intravenous rituximab 375 mg/m2 for 4 doses. The median duration of treatment was 5 cycles (range 1–29). Two DLTs were grade 3 hypercalcemia and grade 4 non-neutropenic fevers. The combination was very well tolerated; the primary grade 3-4 toxicities included neutropenia, lymphopenia and thrombocytopenia. Overall response rate in phase II study was 57.8% with a complete remission (CR) rate of 32.6% and partial remission (PR) rate of 23.9%. Median response duration was 18.9 months (95% CI, 17.0 months – not reached). The median progression-free survival was 13.0 months (95% CI, 8.3–20.8 months). After a median follow-up time of 23.1 months (15.6–53.6 months), the median overall survival was 25.1 months (95% CI, 19.8 months–not reached). Furthermore, this combination induced responses in 2 patients with bulky MCL. In 13 patients who were refractory or intolerable to prior bortezomib treatment, 9 patients achieved responses (6 PR and 3 CR). Out of 46 patients, 12 patients came off protocol and received stem cell transplantation (11 allogeneic and 1 autologous). The response rate was 100% after stem cell transplantation.

Conclusion: Oral lenalidomide plus rituximab is well tolerated and highly effective in patients with relapsed/refractory MCL.

110 COMBINATION OF LENALIDOMIDE WITH R-CHOP (R2CHOP) IS SAFE AND EFFECTIVE AS INITIAL THERAPY FOR AGGRESSIVE B-CELL LYMPHOMAS - A PHASE I/II STUDY

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Background: Lenalidomide was demonstrated to have significant single agent activity in relapsed aggressive B cell lymphoma (J Clin Oncol. 2008;26:4952-7). However, the safety and efficacy of lenalidomide in combination with standard immunochemotherapy is not known.

Methods: A phase I/II study was designed to define the maximum tolerated dose and efficacy of lenalidomide administered on days 1-10 with standard R-CHOP chemotherapy (R2CHOP). Lenalidomide dose escalation levels were 15 mg, 20 mg and 25 mg. All patients received 6 mg pegfilgrastim on day 2 and aspirin prophylaxis. Eligible patients were adults with newly diagnosed CD20 positive diffuse large B cell (DLBCL) or grade 3 follicular lymphoma (FL). Dose limiting toxicity (DLT) was defined as any grade 3 or higher non-hematological toxicity or a hematological toxicity resulting in a delay of the next cycle of chemotherapy. The response was evaluated using PET/CT by standard criteria (J Clin Oncol. 2007;25:579-586).

Results: In the phase I portion, 3 patients received 15 mg, 3 received 20 mg and 6 received 25 mg of lenalidomide. No DLT was found and 25 mg days 1-10 was the recommended dose for phase II. 26 additional patients were enrolled on the 25 mg dose level in the phase II portion for a total of 32 patients at this level. The median age of these 32 patients was 64 years (range, 19-87); 59% (19/32) were males. 28 patients (88%) had DLBCL and 4 (12%) patients had FL grade 3. International prognostic index (IPI) was low, low-intermediate, high-intermediate and high in 6, 13, 11 and 2 patients respectively. 8 patients (25%) experienced a grade 3 non-hematological toxicity and the most frequent were: febrile neutropenia (3 pts), fatigue (2 pts), thrombosis (2 pts), and dehydration (2 pts). Hematological toxicities were: grade 3 and 4 thrombocytopenia (16% and 25% of patients respectively); grade 3 and 4 neutropenia (13% and 75% of patients respectively). For 30 patients evaluable for response the overall and complete response rate was 100% and 83% respectively. Event free survival analysis is ongoing.

Conclusion: Lenalidomide at a dose of 25 mg for days 1-10 is well tolerated when combined with standard R-CHOP21 chemotherapy. The overall and complete response rates are encouraging. Ultimately, a randomized trial will be needed to confirm the benefits of this novel combination.

111 PHASE II TRIAL OF CISPLATIN PLUS ETOPOSIDE PLUS GEMCITABINE PLUS SOLUMEDROL (PEGS) IN PERIPHERAL T-CELL NON-HODGKIN LYMPHOMA (SWOG S0350)

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Introduction: Peripheral T-cell lymphomas (PTCL) account for 8-15% of all non-Hodgkin lymphomas (NHL) have an inferior progression-free survival (PFS) and overall survival (OS) compared to aggressive B-cell NHLs. We *hypothesized* that PTCLs have a short PFS with doxorubicin-containing regimens as they over-express MDR-1/P-glycoprotein (P-gp). We devised PEGS chemotherapy combination (based on ESHAP) to incorporate agents which are not substrates of the P-gp efflux pump. Gemcitabine replaced Ara-C as it has excellent single agent activity in PTCL.

Patients and Methods: Pts with stage II bulky, III or IV [WHO diagnosis of PTCL], both extranodal types (extra-nodal NK/T-cell, nasal; enteropathy; hepatosplenic, subcutaneous panniculitis-like) and nodal (angioimmunoblastic-like, PTCL [NOS], ALCL [ALK-1 negative]) were eligible. Pts with transformed cutaneous T-NHL to PTCL with systemic involvement were eligible. Pts werenewly diagnosed or had relapsed or progressive disease after 1 prior therapy with a non-platinum based chemotherapy (e.g. CHOP). Pts received cisplatin 25 mg/m^2 IV days 1-4, etoposide 40 mg/m^2 IV days 1-4, gemcitabine 1000 mg/m^2 IV day 1 and solumedrol 250 mg IV days 1-4 of a 21 day cycle for a maximum of 6 cycles.

Results: Thirty four pts were enrolled and 33 are evaluable for toxicities, response, progression free survival (PFS) and overall survival (OS). Central pathology review showed pts were either PTCL (NOS) (n= 12, 39% [D1]), ALCL (n= 4, 15%), angioimmunoblastic (n= 5, 12%), or other T-NHL types (n=11, 33%). Majority of pts were newly diagnosed (n=26, 79%). One pt had Grade 5 infection with grade 3-4 ANC that was probably treatment-related. Eleven other pts had Grade 4 toxicity including hematologic (n=7), metabolic (n=3), hemorrhage (n=1), and infection (n=1). Median follow-up among pts still alive is 1.1 years. The estimate of OS at 1-year is 62% (95% CI: 43%-80%) and of PFS at 1-year is 38% (95% CI: 19%-56%). IHC for MDR-1/P-gp expression for 29 pts showed strong positivity in a subset of lymphoma cells in 6 pts and endothelial cells in all cases [C494 antibody].

Conclusions: Overall PEGS treatment was well tolerated by the majority of patients. Further follow-up is required to estimate 2 yr OS, early results are not promising given historical data. The correlation of P-gp expression on endothelial cells to response is under evaluation. Investigation of PEGS may be indicated in combinations with targeted therapy [clinical correlatives funded by Lilly Oncology].

112 FINAL RESULTS OF A PHASE I-II CLINICAL TRIAL OF OXALIPLATIN, FLUDARABINE, CYTARABINE, AND RITUXIMAB (OFAR) COMBINATION THERAPY IN PATIENTS WITH AGGRESSIVE, RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) AND RICHTER SYNDROME (RS)

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Background: To improve the outcomes of the oxaliplatin, fluradabine, Ara-C, and rituximab (OFAR1) regimen (Tsimberidou *et al*, J Clin Oncol, 2008;26:196) we designed OFAR2.

Methods: OFAR2 consisted of oxaliplatin 30mg/m^2 D1-4; fludarabine 30mg/m^2; Ara-C 0.5g/m^2; rituximab 375mg/m^2 D3; and pegfilgrastim 6mg D6. Fludarabine and Ara-C were given on D2-3 (level 1) D2-4 (level 2) or D2-5 (level 3) every 4 wks.

Results: Overall, 102 patients (CLL 67, RS 35) were treated [Phase 1 (''3+3'' design) n=12; Phase II, n=90]. Dose-limiting toxicities were G4 diarrhea and G4 sepsis (2/3 patients, level 3). Level 2 was the maximum tolerated dose (MTD). Of 102 patients, 62% were >60 yrs, 73% had Rai 3-4 stage, 72% β2-microglobulin ≥4 g/dL, 83% unmutated IGVH, 76% ZAP70+, 37% 17p del and 13% had 11q del. The median follow-up was 19 months. Results in patients treated at the MTD are shown in Table.

In patients with 17p del and 11q del, the response rates were 33% and 60%, respectively (median survival, 13 and 15 months). Fifteen patients underwent allogeneic stem cell transplant (SCT) after OFAR2: 9 as postremission therapy (all remain alive; median follow-up from SCT date, 11 months); and 6 as salvage therapy (median survival, 5.8 months).

The most common toxicity was hematologic (neutropenia 76% of patients; anemia 50%; thrombocytopenia 84%).

Conclusion: OFAR2 had antileukemic activity in poor-risk RS and CLL. OFAR2 was superior to OFAR1 in aggressive CLL. OFAR1 was superior to OFAR2 in RS. All patients who underwent SCT as postremission therapy remained alive, confirming our prior observation that patients with RS or relapsed/refractory CLL who respond to treatment should undergo SCT as postremission therapy.

	RS, N = 31		Refractory CLL, N = 65	
Outcome	No. of patients	%	No. of patients	>%
CR	2	6.5	3	4.6
nPR	0	0	9	13.8
PR	9	29	21	32.3
Overall response	11	35.5	33	50.8
	Median (95% CI), months	1-yr	Median (95% CI), months	1-yr
Overall survival	6.6 (4.6, 40+)	29%	22 (14.6, 40+)	68%
FFS	3.0 (1.6, 4.8)	11%	4.5 (3.4, 5.9)	13%

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113 SHORT COURSE FLUDARABINE, MITOXANTRONE, RITUXIMAB FOLLOWED BY ^{90}Y-IBRITUMOMAB TIUXETAN IN UNTREATED INTERMEDIATE/HIGH-RISK FOLLICULAR LYMPHOMA: A PHASE II TRIAL

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Background: An innovative approach combining induction chemotherapy and subsequent consolidation with ^{90}Yttrium-ibritumomab-tiuxetan (^{90}Y-IT) has been upgraded by shortening the chemotherapy duration and by insertion of rituximab, in untreated follicular non-Hodgkin's lymphoma (NHL).

Patients and Methods: A prospective, single-arm, open-label, multicenter, non-randomised phase II trial to evaluate efficacy and safety of a short fludarabine, mitoxantrone and rituximab (FMR) induction followed by radioimmunotherapy, in untreated, intermediate/high-risk, follicular NHL patients. Fifty-five patients were treated using a sequential treatment schedule consisting of 4 induction cycles of FMR chemo-immunotherapy, and a subsequent consolidating single administration of ^{90}Y-IT, 8-12 weeks later. Patients were eligible for radioimmunotherapy if at least in partial response (PR) after induction, with normal platelet and granulocyte counts and a bone marrow infiltration <=25%. Primary study endpoints were response rate and hematological toxicities; secondary endpoints were overall survival (OS) and progression-free survival (PFS).

Results: All patients received 4 induction cycles of FMR, with an overall response rate of 96.4% (38 complete responses, CR, and 15 PR). Fifty-one patients (38 in CR and 13 in PR) received ^{90}Y-IT. By the end of the treatment, 49/55 patients achieved a CR. With a median follow-up of 21.3 months (95%CI 18.7-23.7), the estimated 3-year PFS was 80.6% (95%CI 53.7-92.8) and the 3-year OS 100.0%. Twenty-one patients showed grade ^{3}3 hematological toxicities.

Conclusions: This study has established the feasibility, tolerability, and efficacy of a regimen composed by a short FMR induction with a ^{90}Y-IT consolidation in untreated intermediate/high-risk follicular NHL patients.