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A Phase I Study of Lenalidomide in Combination with Fludarabine and Rituximab in Previously Untreated CLL/SLL

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Lenalidomide is an immunomodulatory drug related to thalidomide that has recently been reported to have significant single agent activity in relapsed CLL, with response rates of 35-50% including some complete responses[1,2]. The mechanism of action is unknown but appears to be immune-mediated given that lenalidomide alters cytokine levels and stimulates T and NK cell function, and lacks cytotoxicity against CLL in vitro[3]. In CLL patients, the administration of lenalidomide can be associated with tumor flare, a syndrome of painful enlarging lymphadenopathy, increased white count, fever, and rash[1,2]. This tumor flare can potentially escalate to become life-threatening, with renal insufficiency, tumor lysis or a systemic inflammatory response[4,5]. The mechanism of tumor flare remains unknown.

Given the high reported response rates with lenalidomide and its theoretical potential to help preserve immune function, we undertook this Phase I study of lenalidomide in combination with fludarabine and rituximab to determine the maximum tolerated dose of lenalidomide in combination with FR, as well as to assess any preliminary signs of efficacy. This prospective study enrolled patients with previously untreated CLL/SLL who required therapy based on 1996 NCI WG criteria. Adequate organ function was required and defined as ANC > 1000 / μl, platelets > 50,000 / μl, creatinine <= 1.5 mg/dL and total bilirubin <= 1.5 mg/dL. All patients tested negative for hepatitis B and C, and none had autoimmune hemolytic anemia. The study was approved by the Dana-Farber Harvard Cancer Center Institutional Review Board, and all patients signed informed consent prior to initiation of therapy.

Six cycles of combination therapy followed by two cycles of consolidation lenalidomide were originally planned. Fludarabine was given at the standard dose of 25 mg/m^2 IV for 3-5 days depending on dose level, with rituximab 375 mg/m^2 on day 1 of each 28 day cycle. In

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DISCLOSURE OF CONFLICTS OF INTEREST

This study was investigator-initiated but received per patient funding and free lenalidomide from Celgene.

order to minimize infusion reactions in the first cycle, all patients received a split dose of rituximab, with 50 mg/m^2 on day 1 followed by 325 mg/m^2 on day 3. Lenalidomide dosing began at 2.5 mg daily for days 1 – 21 of a 28 day cycle. The plan was to start at dose level 1, with three days of fludarabine and 2.5 mg lenalidomide per day, with subsequent dose levels increasing lenalidomide to 5 mg and then 10 mg, followed then by the addition of days 4-5 of fludarabine, and ultimately by escalation of lenalidomide from 10 mg to 25 mg in 5 mg increments. De-escalation from dose level 1 changed the lenalidomide dose to 2.5 mg every other day in dose level -1, and then decreased the fludarabine to two days in dose level -2. All patients received infectious prophylaxis with trimethoprim-sulfamethoxazole and acyclovir (or equivalent). For prevention of deep venous thrombosis, aspirin 81 mg daily was given to patients with platelet counts over 50,000 / μl. During the first cycle of therapy all patients received allopurinol and intravenous hydration with therapy; chemistries including a full comprehensive panel, calcium, phosphate, uric acid and LDH were checked 2-3 times per week and additional IV hydration provided at that time if needed. Tumor flare was treated with ibuprofen, oxycodone, and/or glucocorticoids (a Medrol pak).

The study used a standard 3+3 dose escalation design, with DLT assessed in the first 28 day cycle only. DLT was defined as grade 3 or greater non-hematologic toxicity (except grade 4 for allergic reactions), grade 4 neutropenia or thrombocytopenia, grade 3 febrile neutropenia, or a greater than two week treatment delay in initiation of cycle 2. Hematologic toxicity was assessed according to NCI-WG 1996 criteria, while non-hematologic toxicity was assessed according to Common Terminology Criteria for Adverse Events v3.0 (CTCAE 3.0).

Nine patients were enrolled on this study, as detailed in Table 1. The median age was 59, with a median time from diagnosis of 66.1 mos (12-83 mos). Two-thirds had advanced Rai stage disease, and a majority had unmutated IgVH and were positive for ZAP-70.

Of four patients enrolled at the starting dose level, two experienced dose limiting toxicities. The course of each patient on study is presented in Table 1. The second patient developed tumor flare concomitant with prolonged neutropenia which persisted until day 50 of cycle 1, despite the discontinuation of lenalidomide on day 8 and the use of myeloid growth factors. Because of this DLT, the cohort was expanded to enroll up to six patients, but the third patient on study developed a DLT also, a syndrome of rash, fever, myalgias and rhabdomyolysis (grade 4 creatine kinase) on day 19 of cycle 1. Lenalidomide and simvastatin were discontinued, and the patient tested positive for influenza. Given the influenza and longstanding simvastatin, which may have predisposed to rhabdomyolysis, this patient was rechallenged with study therapy following recovery from influenza and while remaining off simvastatin, but developed a very similar syndrome of rash, fever and rhabdomyolysis after only day 1 of study therapy in cycle 2. He was therefore removed from study for this syndrome, which was clearly related to study therapy. Patient 4 was diagnosed with a secondary malignancy when a pre-existing region of lymphadenopathy progressed on therapy, making this event unlikely related to study therapy.

Given these two DLTs in four patients, the study proceeded to enroll five patients to dose level -1, which included three days of fludarabine, rituximab as described above and lenalidomide 2.5 mg every other day for the first 21 days of a 28 day cycle. Five patients were enrolled on this cohort. Two were able to complete six cycles of study therapy, one of whom went on to two cycles of consolidation. The other three however had significant toxicities, including grade 3-4 cytopenias, grade 3 rash and hand-foot syndrome. Patient 6 did not have adequate platelet recovery to receive cycle 4, despite initial normalization of his platelet count and disease response. Patient 8 had grade 4 neutropenia and thrombocytopenia, causing lenalidomide to be held every cycle after just a few doses, and

mandating per protocol dose reductions to two days of fludarabine. Despite myeloid growth factors this patient still had grade 3-4 cytopenias which mandated dose reductions that caused her to come off study. Patient 9 had recurrent grade 3 rash, grade 3 tumor flare and hand-foot syndrome, as well as neutropenia, in each of the first 3 cycles. Lenalidomide was again held in each cycle and steroids were given, which did resolve the tumor flare in a given cycle, although it recurred in each subsequent cycle. Dose reduction to two days of fludarabine was again required, but due to her recurrent tumor flare symptoms this patient withdrew from the study. A summary of treatment delays, dose reductions and toxicities is shown in Table 2.

The response rate on an intent to treat basis was 56% (90% CI 25-83%). One patient had a CR, one a nodular PR, 3 PRs, and 1 SD. Three patients were not evaluable due to early withdrawal from the study in two cases and a second malignancy in one case. Given the toxicity of the therapy, this level of activity did not justify continuing the study, which was therefore closed to enrollment. Although correlative studies to assess immune cell subsets, CD20 expression and cytokine production were planned and completed on a subset of these patients, the results were difficult to interpret due to the frequent interruption of study therapy and the short duration of time most patients remained on study.

Here we report the results of the first study to combine chemoimmunotherapy with lenalidomide, an immunomodulatory derivative of thalidomide which has been previously shown to have clinical activity in relapsed CLL[1,2]. The mechanism of action of lenalidomide is unknown, but it is not cytotoxic to CLL cells in vitro. Instead lenalidomide has been found to upregulate CD154 as well as CD80, 86 and 95 on the surface of CLL cells[3,6], and to induce T cell activation in patients with CLL[3]. These activities can potentially restore the T cell defect in CLL and increase antibody production[6]. Our hypothesis in undertaking this study was that administering lenalidomide concurrently with fludarabine-rituximab chemoimmunotherapy might result in relative preservation of immune function and enhance activity without toxicity, given their distinct mechanisms of action.

Unfortunately what was found was that even at very low doses of fludarabine and lenalidomide, with rituximab given in split doses initially, this combination was very poorly tolerated when administered concurrently, at least to these patients with a large disease burden. The patient population treated on this study was a difficult one, with two-thirds having advanced stage disease, several with bulky nodal disease and most with adverse prognostic markers. Clinically the coadministration of chemoimmunotherapy, with potential for rapid cytoreduction and myelosuppression, with lenalidomide, with induction of tumor flare reaction and likely activation of the CLL cells themselves, followed also by myelosuppression, proved unstable. Several patients developed serious idiosyncratic reactions, including a febrile syndrome with rash and rhabdomyolysis, and a febrile syndrome with severe nodal pain, rash and hand-foot syndrome, both of which resulted in those patients coming off study. The nature and timing of these reactions was not predictable, and if the patient was rechallenged with the study drugs the reactions recurred. Other patients developed what appeared to be synergistic myelosuppression, with grade 3-4 neutropenia and thrombocytopenia persisting for a week or more despite three days of fludarabine rather than five, lenalidomide 2.5 mg every other day, and myeloid growth factors. These unpredictable reactions and unexpectedly persistent myelosuppression made it difficult to deliver adequate amounts of either fludarabine or lenalidomide, which further resulted in lackluster disease response. Taken together these factors led us to close the study early.

This experience is not dissimilar from previously described severe tumor flare reactions that occurred with single agent lenalidomide at higher doses or in the setting of renal

insufficiency[4,5]. The high tumor burden of our patients may have promoted significant reactions even with low doses of lenalidomide, such that reduction of tumor burden with chemotherapy prior to initiation of lenalidomide might decrease these reactions. An ongoing related study introduces lenalidomide on day 7, and although significant toxicities of neutropenia, skin rash, infection and thrombosis have been observed, tumor flare has been minimal and some patients have tolerated dose escalation[7].

In summary this study found that the concurrent administration of FR with lenalidomide was not tolerable, due to idiosyncratic drug reactions, tumor flare and myelosuppression. Other ongoing studies are assessing the use of lenalidomide for consolidation after a complete course of chemoimmunotherapy, or sequential administration of lenalidomide after chemoimmunotherapy during each one month cycle. Elucidation of the mechanism of action of lenalidomide in CLL will aid in the design of rational combination therapies; for example, if a relatively intact immune system proves to be required for the effectiveness of lenalidomide in CLL, its use after fludarabine-based chemoimmunotherapy may not be as optimal as combinations with immunotherapies or non-myelosuppressive targeted therapies. Consistent with this hypothesis is the report of Ferrajoli and colleagues, who combined rituximab with lenalidomide and found improved activity with decreased toxicity compared to lenalidomide alone[8]. The results of this and other ongoing studies will help to clarify the optimal role for lenalidomide in the therapy of CLL.

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Table 1

Patient Characteristics and Outcomes

Pt	Dose Level		Time Dx to Tx	ALC at Start	Rai	β2M	FISH	IGVH	ZAP-70	Course on Study	Response?
1	1	48M	12 m	6.3	1 Bulky	3.8	Del 11q	UM	Pos	3rd cycle delay and dose reduction for grade 3 ANC; Off study after 3 cycles, poor response	SD
2	1	37M	31 m	319	4 Bulky	7.7	Del 13q	UM	Pos	Cycle 1 Grade 4 ANC – DLT; Off study cycle 1 day 50, persistent neutropenia	Not Evaluable
3	1	59M	66 m	87.6	1	2.5	Normal	Mut	Pos	Fever / rash / myalgia with grade 4 CK – DLT; Recurred at day 2 cycle 2 – off study	Not Evaluable
4	1	66M	18 m	15.0	3	4.1	+12	N/A	N/A	Completed 3 cycles; Off study with newly diagnosed 2nd malignancy, SCCa	Not Evaluable
5	−1	63M	44 m	41.4	2	4.2	Del 13q	N/A	N/A	Completed 6 cycles but no consolidation due to grade 3 AST / ALT during cycle 6 lenalidomide	CR
6	−1	53M	77 m	9.51	4 Bulky	4.2	+12	UM	Pos	Completed 3 cycles, off study due to 4 week treatment delay for persistent grade 2 thrombocytopenia; Consolidation 2 cycles	PR
7	−1	57M	67 m	103.8	3	3.3	Del 13q	N/A	N/A	6 cycles plus 2 consolidation cycles	PR
8	−1	65F	83 m	199.4	4	2.8	Del 13q	UM	Pos	Grade 4 ANC cycle 1 – DLT; Grade 4 ANC / platelets cycle 2 – dose reduced to DL–2; Grade 3 platelets cycle 3, and treatment delay cycle 4 for grade 2 platelets – off study	PR
9	−1	59F	78 m	13.6	3	3.1	Normal	V3-21	Neg	3 cycles, with recurrent tumor flare, grade 3 rash and hand-foot syndrome, and neutropenia; Off study	nPR

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Table 2

Toxicity and Treatment Summary

Median number of cycles	**3(1-6)**
Delay of next cycle	5 / 9 pts
Lenalidomide held in mid-cycle at least once	6 / 9 pts
Dose reduction	4 / 9 pts
Major Toxicities (Grade 3-4)	
Neutropenia	6 / 9 (67%)
Thrombocytopenia	2 / 9 (22%)
Tumor flare	2 / 9
Rash	2 / 9
Hand-foot syndrome	1 / 9
Creatine kinase	1 / 9
ALT / AST	1 / 9
Uric acid	1 / 9
Response rate	5 / 9 (56%) (90% CI 25-83%)