[ABSTRACT WM2.6]

NOVEL AGENTS IN THE TREATMENT OF WALDENSTROM'S MACROGLOBULINEMIA: UPDATE OF WMCTG CLINICAL TRIALS

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Despite advances in therapy, Waldenström's macroglobulinemia (WM) remains an incurable B-cell disorder with elusive complete remissions (8-10%). As such, novel therapeutic agents and combination strategies are needed, particularly if curative efforts are to be pursued. As such, we have prioritized the development of novel as stem cell sparing agents in the treatment of WM.

Proteosome inhibition (WMCTG 03-248, 05-180)

Bortezomib, a stem cell sparing agent, is a proteosome inhibitor which induces apoptosis of primary WM lymphoplasmacytic cells, as well as the WM-WSU WM cell line at pharmacologically achievable levels. Moreover, bortezomib may also impact on bone marrow microenvironmental support for lymphoplasmacytic cells. In a multi-center study of the Waldenstrom's Macroglobulinemia Clinical Trials Group (WMCTG), 27 patients received up to 8 cycles of bortezomib at 1.3 mg/m2 on days 1, 4, 8, and 11. All but one patient had relapsed/or refractory disease. Following therapy, median serum IgM levels declined from 4,660 mg/dL to 2,092 mg/dL (p<0.0001). The overall response rate was 85%, with 10 and 13 patients achieving a minor (<25% decrease in IgM) and major (<50% decrease in IgM) response. Responses were prompt, and occurred at median of 1.4 months. The median time to progression for all responding patients in this study was 7.9 (range 3-21.4+) months, and the most common grade III/IV toxicities occurring in > 5% of patients were sensory neuropathies (22.2%); leukopenia (18.5%); neutropenia (14.8%); dizziness (11.1%); and thrombocytopenia (7.4%). Importantly, sensory neuropathies resolved or improved in nearly all patients following cessation of therapy. In an ongoing trial by the WMCTG, bortezomib has been combined with dexamethasone and rituximab (BDR) for the primary therapy of patients with WM. As part of this study, patients are receiving intravenous bortezomib at 1.3 mg/m2 and dexamethasone at 40 mg on days 1, 4, 8, 11, along with rituximab (at 375 mg/m2) on day 11. Among 23 evaluable patients completing the first 4 cycles of induction therapy, median serum IgM levels declined from 4,830 to 1,450 mg/dL (p<0.0001) and median Hct rose from 29.8 to 37.1% (p=0.0006). The overall response rate was 91% with categorical responses as follows:
CR (n=2); PR (n=13); MR (n=6). Responses were prompt, and occurred at median of 1.5 months. With a median follow-up of 8.1+ (range 2.8-18.6+) months, no responding patients have progressed. The most common grade III/IV toxicities occurring in > 5% of patients were sensory neuropathies (48%); leukopenia (13%); neutropenia (9%); and thrombocytopenia (9%). Notably, 4 of the first 7 patients receiving BDR in this study developed herpes zoster reactivation necessitating prophylaxis with daily valcyclovir (1 gm).

Monoclonal antibody therapy (WMCTG 02-079)

Alemtuzumab is a humanized monoclonal antibody which targets CD52, an antigen widely expressed on bone marrow LPC in WM patients, as well as on mast cells which are increased in the BM of patients with WM and provide growth and survival signals to WM LPC through several TNF family ligands (CD40L, APRIL, BLYS). As part of a WMCTG effort, 28 subjects with the REAL/WHO Clinicopathological diagnosis of LPL,

including 27 patients with IgM (WM) and one with IgA monoclonal gammopathy were enrolled in this prospective, multicenter study. Five patients were untreated and 23 were previously treated, all of whom had previously received rituximab. Patients received 3 daily test doses of alemtuzumab (3, 10, and 30 mg IV) followed by 30 mg alemtuzumab IV three times a week for up to 12 weeks. All patients received acyclovir and bactrim or equivalent prophylaxis for the duration of therapy plus 8 week following the last infusion of alemtuzumab. All patients tolerated test dosing, and completed a median of 33 infusions post test-dosing. Among 27 patients evaluable for response, median Ig levels decreased from 3,665 to 1,495 mg/dL (p<0.0001). The overall response rate was 81%, which included 1 CR (4%), 10 PR (37%), and 11 MR (41%). Hematological toxicities were common among previously treated (but not untreated) patients and included grade 3/4 neutropenia 39%; thrombocytopenia 18%; anemia 7%. Grade 3/4 non-hematological toxicity for all patients included dermatitis 11%; fatigue 7%; and infection 7%. CMV reactivation and infection was commonly seen among previously treated patients and may have been etiological for one death on study. Two other patients also succumbed on study, one related in part to drug therapy for CMV infection and another due to complications of alemtuzumab induced thrombocytopenia and Von Willebrand deficiency.

Signal inhibitors

Inhibitors of Stem Cell Factor Signaling (WMCTG 05-140)

Characteristic of WM is an increased number of mast cells (MC) which are found in association with LPC, and stimulate LPC growth through several TNF-family members including CD40L, APRIL and BLYS. As such, the direct targeting of MC in WM may yield therapeutic results. One important growth and survival factor for MC is stem cell factor (SCF), which signals through CD117. Imatinib mesylate blocks SCF signaling through CD117, and induces apoptosis of WM BM MC and LPC, both of which highly express CD117. As such, we performed a Phase II study of imatinib mesylate in patients with relapsed and refractory WM. Intended therapy consisted of imatinib mesylate which was initiated at 400 mg daily over the first month, and subsequently dose escalated to 600 mg daily for up to 2 years. Dose de-escalation to 300 mg daily was permitted for toxicity. 28 patients with a median of 2 prior therapies have been enrolled on this study. With a median follow-up of 9 months, serum IgM levels for 27 evaluable patients declined from 3,110 to 2,530 at best response (p<0.0001). The overall response rate was 26%, with 2 PR and 5 MR. Responses were prompt, and occurred at a median of 2.1 months. Major treatment related toxicities included anemia, thrombocytopenia, leukopenia and edema and lead to treatment cessation in 9 patients. Importantly, tryptase levels which measure mast cell burden declined from 6.6 to 2.0 ng/mL (at 1 month), and were at 2.9 ng/mL (at 3 months) for 7 evaluable patients. The interim results of this study demonstrate that imatinib mesylate is an active salvage therapy, and may impact on mast cell burden in WM.

Phosphodiesterase inhibitors (WMCTG 05-087)

Inhibition of phosphodiesterase 4 (PDE-4) leads to apoptosis of malignant lymphoma cells. The mechanism by which PDE-4 inhibition leads to apoptosis remains to be defined but may involve dysregulation of cyclic AMP. Sildenafil citrate is a potent phosphodiesterase-5 inhibitor, which also exhibits weak PDE-4 inhibition and is used to treat erectile dysfunction. Interestingly, we and others have observed responses to sildenafil citrate among patients with WM and chronic lymphocytic leukemia (CLL). Moreover, sildenafil citrate induces apoptosis of primary tumor cells from patients with WM and chronic lymphocytic leukemia. In view of these data, the WMCTG conducted a

prospective phase II study of sildenafil citrate in patients with slowly progressing WM who did not meet consensus eligibility for active therapy. Patients on this study were initiated at the dose of 25 mg daily, then dose escalated weekly by 25 mg until they reached the final dose of 100 mg daily. Thirty patients were enrolled, 18 of whom were previously untreated. All patients demonstrated progressing disease prior to enrollment. Patients were evaluable for response after 3 months of therapy. At best response, serum IgM levels declined from 3,550 to 2,965 mg/dL (p=0.007), with 22/30 patients demonstrating a decrease in serum IgM levels (range -4 to -45%). Overall, 5 (17%) patients demonstrated at least a MR, with a median TTP for responders of 6.1 (range 2.5-9.8) months. Therapy was well tolerated, and there were no grade 3/4 toxicities. Future efforts aimed at developing more potent phophodiesterase-4 inhibitors are contemplated. In summary, advances in the biological understanding of WM are yielding newer and more targeted therapies for the treatment of this malignancy and have led to development of several novel agents. Clinical trials further establishing the optimal use of these agents, as monotherapy or in combined therapy are warranted.