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mTOR inhibitors for the treatment of lymphoma

Patients with non-Hodgkin lymphoma (NHL) or Hodgkin disease (HD) who relapse after conventional chemoimmunotherapy and/or stem cell transplantation are usually incurable. New agents are needed for this group of diseases. The phosphatidylinositol-3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway integrates signals from multiple receptor tyrosine kinases and regulates many cellular processes, including proliferation, growth and survival. In lymphoma cells this pathway has been shown to be upregulated.[1] For example, a pathologic hallmark of mantle cell lymphoma (MCL) is the characteristic overexpression of cyclin D1 in the MCL tumor cells.[2] Cyclin D1 is one of the proteins whose translation is under the control of the PI3K signal transduction pathway and is downstream of mTOR.[1] Several drugs are now in clinical use or in trial that inhibit mTOR. The first member of this class of drugs is rapamycin (sirolimus) which was originally isolated from a strain of *Streptomyces hygroscopicus* found in the soil of the Vai Atore region of Easter Island.[3,4] Oral sirolimus is approved for the prophylaxis of kidney transplant rejection. Temsirolimus, a dihydroester of the selective mTOR inhibitor rapamycin (Wyeth Pharmaceuticals), is approved by the US FDA for the treatment of renal cell carcinoma because of its demonstrated anti-tumor activity at a dose of 25 mg IV weekly.[5,6] Everolimus (Novartis) is an oral agent also based on the structure of rapamycin. It is available in Europe as an anti-rejection agent and is undergoing clinical trial in various cancers. As a class, the mTOR inhibitors are generally well-tolerated. The side effects to be aware of are myelosuppression (especially thrombocytopenia), dysgeusia, hyperglycemia and hyperlipidemia and less commonly pulmonary infiltrates, rash, and oral ulcers.

The Mayo Clinic and the North Central Cancer Treatment Group have reported 2 clinical trials of IV temsirolimus for relapsed MCL.[7,8] The first phase II trial tested a dose of 250 mg IV weekly and found a 38% overall response rate (ORR), with 3% complete remissions (CR) and 35% partial remissions (PR).[8] However, in this patient population reversible myelosuppression was substantial with 71% (25/35) of patients experiencing grade 3 and 9% (3/35) grade 4 hematological toxicity. A follow-up study with a similar design tested a low dose of (25 mg weekly) for patients with relapsed MCL.[7] Of 29 patients enrolled, 28 were evaluable for toxicity and 27 for efficacy. The median age was 69

years (range, 51-85), 86% were stage 4, and 71% had ≥2 extranodal sites. Patients had received a median of 4 prior therapies (range, 1-9) and 50% were refractory to the last treatment. The ORR was 41% (11/27; 90% CI: 22-61%) with 1 complete (3.7%) and 10 PR (37%). The median TTP in all eligible patients was 6 months (95% CI: 3-11 months) and the median DR for the 11 responders was 6 months (range, 1-26 months). Hematological toxicities were the most common, with 50% (14/28) grade 3 and 4% (1/28) grade 4 toxicities observed. Thrombocytopenia was the most frequent cause of dose-reduction.

A recently completed phase III trial randomized patients with relapsed MCL to temsirolimus vs. single-agent treatment of the investigator's choice.[9] There were two schedules of temsirolimus used - IV temsirolimus, 175 mg 3x weekly followed by either 75 mg (175/75, arm 1) or 25 mg (175/25, arm 2) weekly.[9] One-hundred sixty two patients were enrolled (54 per arm). Treatment with temsirolimus 175/75 mg resulted in significant improvement in PFS and objective response rate and a trend toward longer overall survival compared with investigator's choice.

Studies of temsirolimus have also been performed for other NHL types.[10] Smith *et al.*[10] also used the 25 mg IV weekly schedule in 82 patients with relapsed NHL. Patients had received a median of 2 prior regimens (range, 1-7), and all but 9 had prior rituximab. The ORR in pts receiving at least one dose of temsirolimus is 35% (26/74) with 25 pts maintaining stable disease.

In summary, single-agent temsirolimus at a dose of 25 mg weekly is an effective new agent for the treatment of MCL. This dose level retains the anti-tumor activity of the 250 mg dose with less myelosuppression. Further studies of temsirolimus in combination with other active drugs for MCL and other lymphoid malignancies are warranted.

Everolimus also has activity in relapsed NHL. The Mayo Clinic and Dana Farber have collaborated on a phase II trial of single-agent everolimus using a starting dose of 10 mg each day. Reeder *et al.* recently reported the results for the patients with aggressive disease.[11] Thirty-seven pts were treated; 20 (54%) with relapsed diffuse large cell (DLC), 14 (38%) with relapsed mantle cell (MCL), 2 high grade, and 1 follicular grade III. The median age was 72 years (range, 45-92). Patients had received a median of 4 prior therapies (range, 1-15). The ORR was 32% (12/37; 95% CI:20-49%) with 1 CR and 11 PR. The ORR was 35% (7/20) in the DLBCL group and 29% (4/14) in the MCL patients. Patients have received a median of 2 cycles (range, 1-16+) of therapy. The median TTP for all 37 patients is 3.1 months. The median DR for the 12 responders is 5.5 months and 5 pts remained progression free at 6 months. Three patients are currently maintaining a response with a median time of 10.5 months (range, 2.9-15.6+months). Everolimus was well tolerated. The incidence of grade 3 anemia, neutropenia, and thrombocytopenia in this heavily pretreated pt population was 11%, 16%, and 30%.

The same trial also treated 17 patients with relapsed HD.[12] The median age of these patients was 37 yrs (range: 2768), with a median of 6 (range, 4-14) prior therapies. Fourteen pts (82.4%) had a prior stem cell transplant (SCT). Pts completed a median of 6 (range, 113) cycles of therapy. Fifteen of 17 patients were evaluable for response as of this analysis. The ORR was 47% (7/15), all PRs. Ten patients are continuing on study while 6 have gone off due to disease progression and 1 due to other reasons.

These results with both temsirolimus and everolimus, in NHL and HD, provide the rationale for additional studies with this novel class of agents and to integrate mTOR

inhibitors into salvage treatment regimens. It also provides proof-of-concept that targeting the mTOR pathway in lymphoma is clinically relevant.

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