



MYELOMA CANADA

MAKING MYELOMA MATTER

Novel Therapies Advance Multiple Myeloma Treatment

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SAN FRANCISCO - A sweep of new agents are poised to deliver what could be a knock-out blow to multiple myeloma, according to the director of the myeloma program at the University of California, San Francisco. Some are second- or third-generation agents in a mainstay class that appear to have less toxicity than and/or overcome resistance to their predecessors, Dr. Jeffrey L. Wolf said at the annual Oncology Congress here. Others come from classes not previously used in this disease.

"There is a rush to develop new drugs in myeloma," Dr. Wolf told attendees. "We [understand] some mechanisms that the disease seems to favour, so we can interfere with those."

The prospects, in turn, are excellent: "We have made such tremendous headway in myeloma, except for those exceptional cases with 17p deletions and some other adverse prognostic features," he said. "As a disease, it seems to be on the ropes."

A Less-Toxic Proteasome Inhibitor

The first-generation proteasome inhibitor **bortezomib** (Velcade) improves myeloma outcomes, but maximizing its benefit will require addressing the peripheral neuropathy that limits its use. Three strategies may lessen this toxicity without compromising efficacy, Dr. Wolf suggested: modestly reducing the standard dose, adjusting the schedule from twice to once weekly, and altering the route of administration from intravenous to subcutaneous.

For example, in patients with pre-treated myeloma, giving bortezomib subcutaneously instead of intravenously results in an identical overall response rate of 52% (Lancet Oncol. 2011;12:431-40). But there are significant reductions

in rates of peripheral neuropathy of any grade (38% vs. 53%) and grade 3 or higher (6% vs. 16%).

"Practically everybody that we see now at UCSF gets subcutaneous [bortezomib]," Dr. Wolf said. It's a great way to go back and treat patients who maybe otherwise have stopped their therapy because of their neuropathy."

Carfilzomib, an investigational next-generation proteasome inhibitor in phase III trials, is showing good anti-myeloma activity and a low rate of peripheral neuropathy. Among patients with pre-treated, relapsed, or refractory disease, carfilzomib monotherapy achieved overall response rates of 42% to 53% in a bortezomib-naive group (ASCO 2011 annual meeting. Abstract 8026) and 21% in a bortezomib-exposed group (Haematologica 2010;95:452 Abstract 1099). Median time to progression was at least 8 months for both.

Dr. Wolf said that unpublished data suggest that the response rate was still 17% specifically among patients who had had progression on bortezomib, "so there appears to be some activity in patients who are already refractory to a prior proteasome inhibitor."

Meanwhile, the rates of grade 1/2 and grade 3 peripheral neuropathy were 6% and 1%, respectively. And only a single patient of the 155 had to stop treatment because of this adverse effect.

When carfilzomib is combined with lenalidomide-dexamethasone (the so-called **CRd regimen**), the overall response rate in patients with pre-treated, relapsed, and refractory disease is 78%, and the rate of complete or near complete response is 24% (ASCO 2011 meeting. Abstract 8025). And, in newly diagnosed myeloma, among 18 patients receiving eight cycles of CRd, the overall response rate was 100%, and the rate of stringent-complete, complete, or near-complete response was 61% (2011 International Myeloma Workshop. Poster P-253). "This is very, very exciting—I don't think we've seen this in any other combination," Dr. Wolf commented. "But these are small numbers of patients; we still need to increase the numbers of patients studied with this combination."

Bortezomib and carfilzomib may soon have company from several investigational proteasome inhibitors available in oral formulations that have shown promise in preclinical testing or have advanced to clinical trials: **CEP-18770** (Cephalon), **ONX-0912** (Onyx), and **MLN-9708** (Millennium).

A Third-Generation IMiD in Trials

Pomalidomide, a third-generation immunomodulatory drug (IMiD), coming after thalidomide (Thalomid), and lenalidomide (Revlimid), is also showing good anti-myeloma activity in clinical trials, according to Dr. Wolf.

Among patients with pre-treated myeloma, the rate of partial or better response when pomalidomide is combined with dexamethasone has ranged from 25% to 42%, depending on the trial and patient population. Adverse events are primarily hematologic.

And in patients who have previously received lenalidomide, the response rate is similar, at 35% (ASCO 2011 annual meeting. Abstract 8067). "So, as with carfilzomib, where there appear to be responses in patients who have prior resistance to bortezomib, it appears that pomalidomide can give us responses in patients who have already had resistance to lenalidomide," he said.

HDAC Inhibitors Show Activity

The histone deacetylase (HDAC) inhibitor **vorinostat** (Zolinza) is approved for treatment of lymphoma. But it is being tested in clinical trials for myeloma, in combination therapy, with promising results, according to Dr. Wolf. Overall response rates have ranged from 40% to 94%, depending on the patient population and combination. Similarly, the HDAC inhibitor **romidepsin** (Istodax) is approved for lymphoma treatment but is also being studied for anti-myeloma activity. And **panobinostat**, an investigational member of this drug class, is being evaluated as a component of combination therapy in phase II and III myeloma trials.

Monoclonal Antibodies Tested

Elotuzumab is an investigational monoclonal antibody directed against CS1, a glycoprotein that is highly expressed on the surface of plasma cells and implicated in myeloma pathogenesis.

In a phase I trial among patients with relapsed or refractory myeloma, the combination of elotuzumab with lenalidomide and low-dose dexamethasone yielded an overall response rate of 82% (ASCO 2011 meeting. Abstract 8076). The rate was 83% among the subset of patients whose disease was refractory to the most recent therapy and 95% among the subset of lenalidomide-naive patients.

The combination of elotuzumab with bortezomib has also been tested in patients with relapsed or refractory myeloma. But the overall response rate with this combination was less impressive, at 48% (ASH 2010 meeting. Abstract 3023).

Other Agents and Pathways

Several other agents are being eyed for roles in myeloma therapy as well. They include **bendamustine** (Treanda), an old drug initially revived for lymphoma treatment; aurora kinase inhibitors (for example, **MLN-8237**); and inhibitors of the mammalian target of rapamycin, or mTOR (for example, **INK-128**).

Additionally, there is considerable interest in agents that target fibroblast growth factor receptor 3 (FGFR3) for one subgroup. "In patients with the 4;14 translocation, FGFR3 is over-expressed," Dr. Wolf explained. "Finding an inhibitor for that or a direct antibody ... may be quite effective in those patients."

Investigators are also assessing the impact of targeting certain signalling pathways, such as the Jak/Stat pathway and the AKT pathway. For instance, a phase III trial is testing **perifosine**, an investigational AKT inhibitor, in combination therapy among patients with relapsed or refractory myeloma (NCT01002248).