Elotuzumab: a monoclonal antibody (mAb)

Elotuzumab (HuLuc63) is a humanized monoclonal antibody (mAb) targeting CS1, a cell surface glycoprotein expressed on myeloma cells, with restricted expressed on natural killer (NK) cells. It has shown activity in a mouse model, enhanced in combination with lenalidomide. Phase I results of 5, 10, and 20 mg/kg dosing were presented. Elotuzumab-related AEs were primarily infusion-related in 89% patients, mostly grade 1 to 2, with no DLT, and MTD was not reached. Median TTP was not reached at a median follow-up of 12.7 months. Elotuzumab saturated the CS1 binding sites in bone marrow myeloma cells at 10 mg/kg. The phase II study objectives were to evaluate the ORR of elotuzumab plus lenalidomide and dexamethasone in patients with relapsed/ refractory myeloma after 1 to 3 prior therapies, and to evaluate doses of 10 and 20 mg/kg. Dosing was weekly for the first 4 cycles, then every other week. Lenalidomide was given at 25 mg and low-dose dexamethasone was administered weekly. Patients also received Solu-Medrol (methylprednisolone) and other drugs to prevent infusion reactions. Patients had received no prior lenalidomide. The safety population of 63 patients received 10 mg/kg or 20 mg/kg doses. Most patients had had a prior transplant, and most had received prior thalidomide. ORR was 90% with the 10-mg/kg dose. The best confirmed response of at least PR occurred in 90% of patients on the 10-mg/kg dose and in 72% of patients on the 20-mg/kg dose. The study was not powered to determine the differences between doses; both doses had a sCR/CR rate of 5%. VGPR occurred in 37% of patients overall, and was 42% for the 10-mg/kg dose. Patients with higher beta-2-microglobulin (β2M) responded. Median time to best response was 2 months for both arms. Median follow-up was 4.9 months, and median PFS was not reached. The AE profile was mostly as expected with lenalidomide and dexamethasone. Higher grade hematologic AE were as expected and were manageable. Elotuzumab-related AE included fatigue and low-grade fever and were manageable. There was no treatment-related mortality. Infusion reactions occurred in 89% in the phase I portion of this trial, but with proper management were cut in half in phase II (typical of mAbs). The 10-mg/kg dose is recommended for the open-label phase III trial to start next year.

Other mAbs in development

DR (death receptor) anti-TRAILR (tumor necrosis factor-alpha-related apoptosis-inducing ligand receptor) mAbs kill myeloma cells. One study analyzed two mAbs: mapatumumab, which is anti-TRAIL-R1 (DR4), and lexatumumab, which is anti-TRAIL-R2 (DR5). Regulation of DR4 and DR5 are different. Mapatumumab kills p53 mutant cell lines. Death induced by mapatumumab depends only on the extrinsic pathway of apoptosis, involving caspase. In contrast, lexatumumab kills p53 wild-type myeloma cell lines, which express more DR5 than mutant lines. Melphalan increases DR5 in wild-type p53 lines. In p53-mutant lines melphalan does not increase DR5 or p53. Melphalan doesn't affect DR4 expression; it increases lexatumumab killing of wild-type p53 lines, and does not increase mapatumumab killing of either wild-type or mutant cell lines. p53 activation increases only DR5 expression and sensitivity. Mapatumumab could be of interest in combination with melphalan for patients with wild-type p53 and lexatumumab could be of interest for patients with p53 mutations. These agents are in clinical trials but no results are available at this time.

Other new targeted therapies in early development

mTOR (Mammalian Target of Rapamycin): Final results were presented from the phase I/II trial of weekly bortezomib in combination with temsirolimus (CCI-779) in relapsed or relapsed/refractory myeloma in patients refractory to bortezomib. The PI3K (phosphoinositol 3 kinase) pathway is important in enhancing cell survival by stimulating cell proliferation and inhibiting apoptosis. mTOR inhibitors may overcome resistance to bortezomib because they are synergistic with bortezomib in vitro and in co-culture. All of the 63 patients (20 in phase I and 43 in phase II) had at least one prior therapy and were heavily pretreated with dexamethasone; most had received thalidomide, bortezomib, and lenalidomide. There was a high percentage had ISS stage III disease. IV temsirolimus was given at 15 to 25 mg weekly on days 1, 8, 15, 22, and 29 on 35 day cycles. Bortezomib at 1.3 to 1.6 mg/m2 was given weekly on days 1, 8, 15, and 22. Dexamethasone was not permitted. Phase I was a dose-escalation study; the most common toxicity was thrombocytopenia. In phase II, toxicities included thrombocytopenia and fatigue; there was no sensory neuropathy due to temsirolimus or weekly bortezomib. ORR in phase II was 40% excluding unevaluable patients. In patients with bortezomib-resistant disease the ORR was 20%; with bortezomib-sensitive disease the ORR was 53%. Median PFS for phase II was 5 months. Median TTP was 5.7 months. The combination is active and warrants further evaluation.

Dual-targeting of ?TORC1 and ?TORC2: In vivo antitumor activity of TORC1 (which contains raptor) and TORC2 (which contains rictor) inhibition, including phosphorylated proteins in the activation pathway, was analyzed. TORC1 and TORC2 both are activated by growth factors, cytokines, and PI3K/Akt. TORC1, but not TORC2, is inhibited by rapamycin and its analogues. Deptor is an mTOR-interacting protein expressed by myeloma cell lines. Downstream targets of TORC1 include Erk, and of TORC2 include pAkt and Akt. TORC2 is activated in myeloma. INK128 is a novel, orally available small molecule that inhibits TORC1 and TORC2. INK128 inhibits the proliferation of myeloma cells and plasma cells but not normal lymphocytes or granulocytes. Inhibition of TORC1 and TORC2 induces apoptosis and overcomes the bone marrow microenvironment effect. The growth of myeloma cells, with or without stromal cells, is not inhibited by rapamycin but is inhibited by INK128. The mTOR pathway and downstream targets are active in myeloma cells. TORC1 and TORC2 inhibition induces apoptosis and has a higher effect in cell cycle arrest, abrogates the protective effect of the bone marrow microenvironment, and inhibits tumor cells without toxicity to other cells. A phase I trial of TORC1 and TORC2 inhibition is to be initiated.

CDK4/CDK6: PD-0332991 is a selective, reversible, orally bioavailable inhibitor of cyclin-dependent kinases (CDK) 4 and 6. CDK4/6 are positive regulatory factors involved in the cell cycle that are associated with phosphorylation of Rb and increasing cell proliferation with disease progression in myeloma. PD-0332991 has a low toxicity. Induction of prolonged G1 arrest by inhibition of CDK4/6 may disrupt coupling of gene expression from the cell cycle, thereby sensitizing cells to killing by other agents (e.g. lenalidomide or bortezomib). Because this inhibition is reversible, release from G1 arrest may synchronize cells and improve killing by bortezomib. A phase I dose escalation study of PD-0332991 determined the dose for the phase II portion of the trial. Patients with symptomatic relapsed/refractory myeloma after more than one treatment were Rb positive and had disease with a

high proliferation rate. Schema A administered PD-0332991 daily for 21 days plus bortezomib and dexamethasone, but DLTs required dose reductions. Schema B administered PD-0332991 daily for 11 days plus bortezomib and dexamethasone, and DLT occurred at the first dose escalation. So the dose of PD-0332991 for phase II was determined to be 100 mg (along with 1.0 mg/m2 bortezomib and 20 mg dexamethasone).

PD-0332991: The hypothesis tested in another study is that induction of prolonged G1 arrest in myeloma cells by inhibition with PD-0332991 would lead to synchronous cell cycle progression into S phase upon release of the G1 block, at which point the myeloma cells would be sensitized to cytotoxic killing by bortezomib or lenalidomide. Lenalidomide targets myeloma cells by inducing late G1 arrest (prior to evidence of apoptosis) that is initiated by p21, a negative regulator of the cell cycle, independently of Rb. Lenalidomide and PD-0332991 have an additive effect of reduction of IRF4 (interferon regulatory factor 4), a critical myeloma cell survival factor. Inhibition of CDK4/6 enhances lenalidomide killing of 70% of primary bone marrow myeloma cells via enhanced apoptosis.

Other targets

Transcription factor Sp1 is a novel target for therapy in myeloma. Nuclear Sp1 protein expression is high in myeloma cell lines; it is mostly cytoplasmic in peripheral blood mononuclear cells. The interaction of myeloma cells with bone marrow stromal cells (BMSC) increases the expression and functional activity of Sp1, which regulates cell growth and survival in myeloma. It is inhibited by Erk inhibitors but not by Akt inhibitors. Genetic inhibition can be accomplished using siRNA (small interfering RNA) and shRNA (short hairpin RNA) and small molecule inhibitors. Knock down of Sp1 using siRNA decreases myeloma cell proliferation. The small molecule terameprocol (TMP) is a pharmacologic inhibitor of Sp1 activity, decreasing myeloma cell proliferation, overcoming the growth promoting effect of BMSC, and leaving the BMSC still viable. TMP induces G2/M cell cycle arrest and apoptotic cell death, and also induces mitochondrial apoptotic pathway activation and decreases the expression of survivin and Cdc2, which are Sp1 survival genes. In vivo interference with Sp1 activity delays tumor growth and prolongs survival in three murine xenograft models. TMP inhibits Ki67 expression, increases caspase 3, and abrogates tumor growth in the SCID/hu mouse model. Treatment with lenalidomide also increases Sp1 activity in myeloma, and has synergistic activity with TMP in myeloma cells even in the presence of BMSC. Changes in Sp1-responsive gene levels predict survival in myeloma. Upregulation of Sp1 responsive genes correlates with a poor clinical outcome. Therefore, Sp1 is a novel target for therapy in myeloma.

BP-1-102 is a novel direct small-molecule inhibitor of STAT3. BP-1-102 is minimally active against STAT1 and is active against STAT5, but is most active against STAT3. BP-1-102 potently inhibits myeloma cell line viability in the 14 lines tested, and induces apoptosis in the 4 myeloma cell lines tested. It is not cytotoxic to non-transformed cells at doses that have antimyeloma activity. BP-1-102 suppresses STAT3 target genes but not non-target genes. Bone marrow stroma confers modest resistance in co-cultures but apoptosis is still seen. BP-1-102 preferentially induces apoptosis of CD138+ primary myeloma cells from patient bone marrow. Studies to evaluate the in vivo efficacy of single agent BP-1-102 are ongoing. Data suggest STAT3 is a viable therapeutic target in myeloma and BP-1-102 has demonstrates substantial anti-myeloma pre-clinical activity.

Conclusions

The trend of increased survival for patients with myeloma that began in the era of novel agents (bortezomib, lenalidomide, and thalidomide) is continuing. Future regimens are likely to be based on combination therapies with unique mechanisms of action and non-overlapping toxicities. Tailoring of therapy to individual patients' needs is advancing, and is including patient quality of life.

Relapsed/refractory disease is the testing ground for all new drugs, as there is a clear need to have something for patients after they have exhausted their available therapeutic options.

Several newer agents and therapies are being investigated for myeloma, and they are showing great promise.

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Special Advocacy Workshop for Patients and Caregivers

At ASH, the IMF Advocacy team hosted its first in-person advocacy tutorial for patients and caregivers. The half-day workshop took place on December 2, with nearly 40 individuals in attendance. The aim of the tutorial was to help guide individuals to join grassroots efforts to advocate for critical health issues that affect the myeloma community. Training topics included Advocacy 101, building relationships and communicating with legislators, an overview of IMF advocacy efforts, and much more. For more information about the IMF advocacy program go to myeloma.org and click on the "advocacy" tab.