DEVELOPMENT OF ANGIGENESIS INHIBITORS FOR THE TREATMENT OF CANCER

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Over 35 years ago, Dr. Judah Folkman pioneered the idea that solid tumors cannot grow beyond 2-3 mm³ without the formation of new blood vessels. Since then, much effort has been devoted to inhibiting angiogenesis as a means of controlling tumor growth. D'Amato et al. demonstrated that thalidomide inhibits basic fibroblast growth factor (bFGF)-induced angiogenesis in the rabbit cornea model. The antitumor activity of thalidomide has been evaluated in numerous clinical trials with mixed results. It is now considered standard of care for the treatment of multiple myeloma. In 2001, we reported the results of a randomized phase II trial of thalidomide in patients with androgen-independent prostate cancer (AIPC)⁴. Expanding on this observations, we chose to combine thalidomide with docetaxel, an agent with known activity in this disease. The median overall survival in the docetaxel alone group was 14.7 months compared with 25.9 months for the combination arm (p=0.041). We recently conducted a trial to determine if thalidomide improves progression-free survival (PFS) after limited androgen deprivation therapy (ADT) in patients with biochemical recurrent prostate cancer. This was a randomized, double-blind, placebo-controlled, cross-over study in patients after local definitive therapy. Patients were randomized to oral thalidomide (Th) or placebo (P) in a blinded fashion following 24 weeks of LHRH-A [designated oral phase A (OPA)]. Baseline and monthly PSA were obtained while on thalidomide or placebo, until rise to baseline PSA or rise of PSA to ≥ 5 ng/mL, whichever occurred first. LHRH-A was then re-initiated. After a second 24 weeks of LHRH-A, oral treatment then commenced with the opposite agent (Th to P or P to Th), continuing until PSA progression, designated as [(oral phase B (OPB)]. 159 patients accrued; 79 randomized to thalidomide and 80 to placebo in OPA. Median PFS during OPA was 15 months for thalidomide arm compared to 9.6 months for placebo arm (P=0.21). 103 patients proceeded to OPB, of whom 51 patients received thalidomide and 38 patients received placebo. Median PFS during OPB for the thalidomide arm was 17.1 months versus 6.6 months for the placebo arm (P=0.0002)².

In conclusion, we are optimistic that better defining the group of patients who will most likely to respond to novel agents, like thalidomide, will eventually lead to real progress in the treatment of this disease and that thalidomide has a role in controlling angiogenesis in solid tumors.

References:
