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RESEARCH HIGHLIGHT

Stromal targeted therapy in bone metastatic prostate cancer: promise delivered

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The ability of epithelial neoplasms to evade both hormonal and cytotoxic therapies is self-evident as the common carcinomas (lung, stomach, breast, colon and prostate) at their metastatic stage are rarely curable with current therapies. Though the precise reasons for incurability are debated, virtually all agree that tumor genetic heterogeneity makes eradication of the tumor difficult given 'Darwinian' selection processes that are associated with the emergence of drug-resistant cellular clones.[1]

Stromal-targeted therapy has an advantage over direct tumor cell-targeted therapy in that stroma is relatively stable from a genomic perspective. However, the promise of stromal-targeted therapy in prolonging survival in metastatic tumors has been limited outside of the anti-angiogenic agents (such as bevacizumab and sunitinib) in highly selected settings. Palliative effects of bone-seeking radiopharmaceuticals such as samarium-153 lexidronam and strontium-89 chloride are well documented, but limited data with these stromal targeted agents support anti-tumor effects sufficient to alter survival.

The landscape has now changed. A recent large (900 patients) phase III placebo-controlled trial (NCT00699751) with six doses (every 4 weeks) administered of radium-223 (Alpharadin) in bone metastatic castrate-resistant prostate cancer (CRPC) has reported top-line positive results with overall survival as the primary endpoint.[2] The trial was terminated early by the data monitoring committee at an interim overall survival analysis because of reaching a pre-specified stopping point. The hazard ratio for overall survival was 0.699 (P=0.0022). Median survival in the control (placebo) and experimental arms were 11.2 and 14.0 months, respectively. All patients in the trial received the best supportive care which included various secondary hormonal manipulations and palliative external beam radiotherapy. Chemotherapy was not allowed, while subjects were under study. Toxicity in this phase III trial has yet to be reported in detail.[2] In a prior randomized phase II trial of radium-223 utilizing four doses every 4 weeks, toxicity was minimal and essentially restricted to mild and reversible myelosuppression and constipation.[3]

Bone-seeking radiopharmaceuticals are administered by intravenous injection in the outpatient setting. They are cleared rapidly from circulation and deposited on the surface of newly formed bone-stromal matrix which is laid down at the interface between tumor metastases and normal skeleton.[4–6] This bone matrix also comprises part of the stroma within sclerotic metastases and, hence, is in intimate apposition to the bone-metastatic tumor cells. The interactions between bone and metastatic lesion result in a vicious cycle which creates micro-environmental changes that support exuberant tumor growth.[7] Uptake (per gram) of bone-seeking radiopharmaceuticals in bone metastases may be up to 10- to 20-fold higher than that in normal bone and uptake in normal bone is at least 75-fold higher than that in any soft tissue.[4,8] This selectivity of uptake in bone lesions coupled with the short path length of radiation emissions results in minimal radiation exposure to normal organs and tissues.[4,9]

Radium-223 binds to the newly formed bone-stroma in the micro-environment of osteoblastic metastases and its decay results in the emission of a series of alpha-particles. Owing to their mass and charge characteristics, alpha-particles deposit their considerable energy over a very short path (~100μm) which makes them not only more toxic per unit dose of radiation delivered than other forms of anti-cancer radiation (such as gamma rays or beta particles) but also much less impacted by factors such as dose rate and tissue oxygenation.[10] When using radium-223, both tumor and stromal cells are destroyed in the immediate area surrounding radionuclide deposition. The double-strand DNA breaks induced by the alpha-particles are highly lethal given that this form of DNA damage is essentially un-repairable.[11] In clinical studies, anti-tumor effects can be measured by tumor marker declines (such as prostate-specific antigen), whereas bone stromal effects can be measured by declines in bone-specific alkaline phosphatase and urine -*N*-telopeptide. Both anti-tumor and anti-stromal effects are clearly described after radium-223 administration.[3]

The trial with radium-223 is now the sixth phase III trial to demonstrate an advantage in metastatic CRPC, a remarkable fact considering that this disease has been so recalcitrant to therapy for so long. These trials are shown in **Table 1** along with their control groups, hazard ratios and survival findings. We note that comparing phase III trials is hazardous without understanding inclusion and exclusion criteria, control treatments, concomitant treatments and trial design (including 'crossovers'). Full details of each trial are beyond the scope of this brief perspective. Suffice it to say that docetaxel trials were the first in CRPC to demonstrate a survival advantage and docetaxel in combination with prednisone was approved in 2004 as 'first-line' therapy in metastatic CRPC.[12,13] In the phase III study of sipuleucel-T, treatment was restricted to asymptomatic or minimally symptomatic metastatic CRPC patients without evidence of visceral spread.[14] Most, but not all of the sipuleucel-T-treated patients

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Table 1 Phase III trials in metastatic castrate-resistant prostate cancer (CRPC) reporting a benefit in overall survival

Reference	*Trial design: experimental and control arms*	*Median survival (months)*	*Prolongation in median survival*	*Hazard ratio*
Petrylak *et al.*[12]	Docetaxel+estramustine *vs.* mitoxantrone+prednisone	17.5 *vs.* 15.6	1.9	0.80
Tannock *et al.*[13]	Docetaxel+prednisone *vs.* mitoxantrone+prednisone	18.9 *vs.* 16.5	2.4	0.76
Kantoff *et al.*[14]	Sipuleucel-T *vs.* 'unactivated' antigen-presenting cells	25.8 *vs.* 21.7	4.1	0.78
de Bono *et al.*[15]	Cabazitaxel+prednisone *vs.* mitoxantrone+prednisone	15.1 *vs.* 12.7	2.4	0.70
de Bono *et al.*[16]	Abiraterone+prednisone *vs.* placebo+prednisone	14.8 *vs.* 10.9	3.9	0.65
Press release[2]	Radium-223/best supportive care *vs.* placebo/best supportive care	14.0 *vs.* 11.2	2.8	0.70

were chemo-naive. The cabazitaxel[15] and abiraterone[16] trials were specifically conducted in the post-docetaxel metastatic CRPC setting. For the abiraterone and cabazitaxel patients, disease progression despite prior docetaxel was mandated as a condition for trial enrollment. Radium-223 was studied predominantly in patients post-docetaxel judged unsuitable for additional chemotherapy at the time of trial enrollment (though patients refusing chemotherapy were also eligible).[17] Interestingly, other than the two molecularly related taxanes (docetaxel and cabazitaxel), each of the other agents capable of prolonging survival in CRPC are both structurally and mechanistically distinct.

Initial success with combination chemotherapy in oncology was built upon the principal of combining agents with distinct mechanisms of action and non-overlapping toxicities. Success in Hodgkin's disease was the first proof that this approach could result in curative therapy for widespread solid tumors.[18] Given the multiplicity of new agents in CRPC, it is now time to define optimal therapeutic combinations. It is our view that this is likely to result in a major survival impact. Given both the unique mechanism of action and the relative lack of reported toxicity for radium-223, we regard this agent as an excellent partner in the new era of combination therapy for metastatic CRPC.

Disclosures:

Ø.S.Bruland: a patent holder on radium-223, a minor stock holder of Algeta ASA and member of their Scientific Advisory Board.

Oliver Sartor: Consultant and Investigator for Algeta.

William Goeckeler: Patent holder for samarium-153 lexidronam.

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