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TAT-10 Special Lunchtime Seminar: Radium 223 from Bench to Bedside, and Future Directions for Targeted Alpha Therapy

Kanazawa, Japan (UroToday.com) Dr. Joe O'Sullivan, a Professor of Radiation Oncology at Queen's College, briefly reviewed the history of radiation treatment of cancer (and prostate cancer in particular) beginning with Radium treatment only eight years after its discovery by the Curies. A landmark paper on radioactive phosphorous treatment of bone-metastatic prostate cancer was published in the journal Lancet in 1964. More recent internal treatments have concentrated on calcium analogs that are directly absorbed in the bone tumor, starting with Sr98, a beta emitter. Single agent beta emitters showed some (~50 %) palliative response but no benefit for overall survival.

The benefits of targeted alpha therapy have been recognized for some time, but the picture radically changed with the FDA approval of Ra223 dichloride in May 2013. Ra223 has an 11.4 day half-life which is a good match for distribution in the body for clinical applications. The decay chain includes four alpha emitters depositing a total of 93.5% of the decay energy. The very high linear energy transfer (LET) contributes to tumor cytotoxicity through irreparable DNA double-strand breaks.

Dr. O'Sullivan discussed the early clinical trials including three with recruits in Belfast: the BC1-04 trial with 122 mCRPC patients, the ALSYMPCA trial, and the iEAP trial. The Phase 3 ALSYMPCA trial involved 921 patients, randomly divided 2:1 into Ra223 treatment and placebo. Each group additionally also had best standard of care. All patients had confirmed mCRPC, no visceral metastases, >= 2 bone metastases, and were either post-docetaxel or unfit for docetaxel. Subgroups were identified on the basis of: total ALP (<220 U/L vs >= 220 U/L), bisphosphonate use (yes or no), and prior docetaxel use (yes or no). Patients were assessed starting at 6 months followed by 2-4

months out to 36 months. The primary endpoint was overall survival but a number of secondary endpoints (such as ALP response, PSA response, safety, and quality of life). The Ra223 patients showed a 3.6 month longer overall survival compared to placebo (14.9 vs 11.3 months). Ra223 also showed a longer time to first symptomatic skeletal event (15.6 vs 9.8 months). There was little difference in the most common side effects (anemia, bone pain, nausea, diarrhea) in the two patient populations.

Dr. O'Sullivan outlined the standard treatment paradigm of layering therapy as the disease progresses from asymptomatic to symptomatic mCRPC with immunotherapy -> radium therapy -> chemotherapy on top of continuing second generation androgen pathway inhibitors, traditional androgen-deprivation therapy, and best supportive care. Several recent trials have shifted the paradigm such that:

Docetaxel is introduced at the outset concurrent with androgen deprivation therapy. If ADT fails and the mCRPC patient is asymptomatic, Sipuleucel-T, abiraterone acetate, or enzalutamide can be added to the ADT therapeutic backbone, hence the term therapeutic layering or layering therapy. As soon as the patient is mildly symptomatic, Ra223 is started and continued for 6 cycles.

New trials could shift the paradigm again in the coming year. If successful, they suggest adding abiraterone at the outset and continuing it in conjunction with Ra223 therapy. The implications of these changes in the therapeutic landscape are increased overall survival and challenges in current trial endpoints.

Other new therapies could emerge from on-going trials. For example, Ac225 conjugated to PMSA shows great promise [see Morgenstern's contribution to this symposium] although side effects to the salivary glands are currently problematic.

In terms of new radioisotopes, Th227 with a half-life of 18.7 days is an alpha-emitting parent of Ra223 so in principle could add another alpha to the tumor site. Pre-clinical studies are investigating various conjugates for Th227 including PSMA for prostate cancer.

Dr. O'Sullivan concluded on a positive note envisioning a personalized therapy era and calling for more ambitious treatment of metastatic castrate-resistant prostate cancer (mCRP).

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