Managing Castrate Resistant Metastatic Prostate Cancer

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There are better prostate cancer treatments ahead which will be better than hormone treatment, better than chemotherapy, and better than Provenge. It is not the drugs that matter but rather you and your compassion and how you treat your patients. In considering the use of other chemotherapeutics, several things are important in a patient with metastatic prostate cancer. Hormonal treatment is probably the least toxic treatment we can give to patients. I still use hormonal therapy but it is a drug of diminishing efficacy: it works but not as well anymore. If testosterone is under 50, the patient is castrate resistant.

Mitoxantrone and prednisone was the palliative treatment in the past. Docetaxel q. 3 weeks is a standard chemotherapy treatment for prostate cancer. Here is the SWOG9916 and TAX327 data, both of which showed a 20-24% survival benefit after two-and-a-half to three months. These patients are living a meaningful life. Abiraterone is a good drug which blocks several pathways, and blocks the intra-prostatic production of testosterone, and blocks the adrenal production of testosterone; it works in both chemo-naïve patients, chemo-treated patients, and multiple treated patients as far as PSA.

MDB3100 is an intra-nuclear blocker of testosterone, currently undergoing phase 3 trials in metastatic, castrate resistant patients who have received one prior chemotherapy and progress; the agent works in chemo-resistant and androgen-resistant tumors. We have not had a standard of care after progression on chemo; as oncologists, we keep patients going on different chemotherapies. We tried mitoxantrone, ixabepilone, novel taxanes, combinations of two and three drugs but with no difference in survival. There is good palliation and response but only short-term. Recently approved in July was carbazitaxel, the first drug in a randomized setting with good performance status which showed improved three-month survival, quality of life, and pain; after two years, patients are actively able to live one year. This drug is tolerable but side effects include febrile neutropenia. Drug combinations have been used; docetaxel and calcitriol did not work in phase 3. Docetaxel and thalidomide were used; lenalidomide is being studied in second line. Other drugs were studied in second line after chemotherapy. Carbazitaxel is a drug that is here to stay and will be the next gold standard for future trials in second or third line.

Bevacizumab slows blood vessel growth. Avastin is approved for colon cancer, breast cancer, and lung cancer. This was tested in metastatic prostate cancer with no survival advantage. Here are other antiangiogenic drugs, and here is another TKI oral drug. We know endothelin is important for metastases; one such drug, ZD4054, improved overall

survival in phase 2, and is currently undergoing phase 3 study. This is the bone drug discussed earlier. The RANK ligand pathway is important: we make bones and destroy bones in prostate cancer, and if we can slow down building and breaking bone, we can decrease skeletal events. The standard drug approved for this is Zometa or zoledronic acid, which decreases the chance of skeletal events in patients with metastatic castrate prostate cancer to the bone; this is the second drug. Lenalidomide at this point is a dream drug. For the management of metastatic castrate resistant prostate cancer, the currently approved therapy is carbazitaxel. In sum, in the metastatic setting, we have better, more powerful drugs; the challenge is to conduct well designed phase 3 trials that would optimally be used in patients to improve symptoms and hopefully survival.