EDITORIAL

The Left Shift in Drugs for Advanced Prostate Cancer

For most physicians, the term "left shift" is about the laboratory results of a CBC with differential. In a normal sample, the white blood cells are mostly represented by the mature cellular elements. In this setting, the left shift refers to an increase in the population of immature precursor cells, often due to infection. The term left shift in the clinical laboratory is historic as it refers to the days when white blood cells were viewed under the microscope and counted manually. The manual counting device was set up with the most mature white blood cells keys on the right-hand side and immature cells counting buttons were on the left. Hence, the origins of the "left shift". Before asking what this has to do with prostate cancer, we need to review another clinical medicine concept known as the "prostate cancer clinical states model".

Several years ago, Dr. Howard Scher and the Prostate Cancer Working Group (PCWG) developed the concept of the prostate cancer clinical states model.[1] On the left side of this disease model was early, newly diagnosed, localized prostate cancer. As you move to the right in the model, you move through various disease states: PSA recurrence, differing manifestations of metastatic disease and ultimately to metastatic, castrate resistant prostate cancer (mCRPC). In this prostate cancer clinical states model, anything on the left side refers to early stages of prostate cancer and to the right are the later, more difficult to manage stages of disease.

Over the last 20 years, there have been over a dozen new agents or combinations of agents that target mCRPC. There has also been a recent trend in clinical trials with subsequent approvals for drugs originally developed for mCRPC being used in earlier stage disease. Using our prostate cancer clinical states model, use of these medications is "shifting to the left". To cite one of the most recent examples of the left shift in advanced prostate cancer drugs is the newest 2023 FDA approval of enzalutamide. Originally approved for mCRPC, it was next approved for metastatic castrate sensitive prostate cancer (mCSPC). Based on the results of the EMBARK trial, enzalutamide has now shifted even further to the left with approval for use in non-metastatic castrate sensitive prostate cancer (nmCSPC).[2]

The shift to the left in prostate cancer appears to be a good thing with these and other trials and approvals indicating early use of other androgen receptor pathway blockers may slow progression from MO to M1 disease.[3] In addition to the early use of antiandrogens, several large phase 3 studies have demonstrated the utility of early chemotherapy with docetaxel. Apalutamide, another androgen receptor pathway blocker approved for both mCSPC and nmCRPC, is being studied as a neoadjuvant and adjuvant in high risk radical prostatectomy trials.

However, some caution is needed as the early and long term use of these agents may create new challenges. The incidence of treatment-related neuroendocrine prostate cancer, a poor prognosis sub-type of prostate cancer, increases after androgen ablation and is most pronounced when the newer androgen receptor pathway inhibitors are used.[4] How our earlier interventions over the long term may impact the biology of prostate cancer is uncertain. What are the long term side effect profiles and potential financial impacts? This is an area deserving of ongoing attention as we continue the left shift of drugs originally shown to benefit men with mCRPC. Based on the series of well-done clinical trials to date, the advantages of early use of medications for advanced prostate cancer in delaying progression and extending survival in men with high-risk prostate cancer are significant and welcomed.

In late 2023, we may have the most extreme left shift imaginable: The LuTectomy. This is a Phase I/II study of upfront [177Lu]Lu-PSMA-617 prior to radical prostatectomy in high risk, localized prostate cancer.[5] The intent of this preliminary trial was to simply investigate the dosimetry, safety, and efficacy of this radiotherapeutic agent currently approved for mCRPC that has failed multiple standard therapies. With further study, the utility of [177Lu]Lu-PSMA-617 as an effective agent to treat early stages of prostate cancer, perhaps using multiple or alternative dosing regimens, remains an open question. This LuTectomy trial and other studies underway demonstrate that the left shift is alive and well in the management of prostate cancer. These approaches represent the ongoing studies of innovative strategies designed to have a positive impact in men with high risk prostate cancer.

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References

1. Scher HI. Building on prostate cancer working group 2 to change the paradigm from palliation to cure. *Am Soc Clin Oncol Educ Book* 2014:e204-e212.
2. Crawford ED, Andriole G, Freedland SJ et al. Evolving understanding and categorization of prostate cancer: preventing progression to metastatic castration-resistant prostate cancer: RADAR IV. *Can J Urol* 2020;27(5):10352-10362
3. Freedland SJ, de Almeida Luz M, De Giorgi U et al. Improved outcomes with enzalutamide in biochemically recurrent prostate cancer. *N Engl J Med* 2023;389(16):1453-1465.
4. Dhavale M, Abdelaal MK, Alam ABMN et al. Androgen receptor signaling and the emergence of lethal neuroendocrine prostate cancer with the treatment-induced suppression of the androgen receptor: a literature review. *Cureus* 2021;13(2):e13402.
5. Eapen RS, Buteau Jackson P et al. Administering [177Lu]Lu-PSMA-617 prior to radical prostatectomy in men with high-risk localised prostate cancer (LuTectomy): a single-centre, single-arm, phase 1/2 study. *Eur Urol* 2023:S0302-2838(23)03087-7.