Prostate Cancer News, Reviews & Views

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Optimal chemohormonal sequencing for mCRPC MAY be Taxotere->Zytiga->Jevtana->Xtandi

(1) Taxotere (docetaxel) first

In a retrospective study presented at the Society for Urologic Oncology meeting, researchers at the Mayo Clinic reported on 112 patients with metastatic castration-resistant prostate cancer (mCRPC).

- Group A (80 men) had docetaxel (Taxotere) followed by one of the second-line hormonal therapies: either abiraterone (Zytiga) or enzalutamide (Xtandi)
- Group B (32 men) had a second-line hormonal therapy followed by Taxotere.
- Bone metastases were more common in Group B (87%) than Group A (58%)

Three-year survival was:

- cancer-specific survival: 87% Group A vs 64% Group B
- overall survival: 82% Group A vs 61% Group B
- results were similar for men with high volume metastases, excluding those with lymph node-only

This was not a prospective randomized clinical trial. It reaches a different conclusion from a couple of earlier retrospective analyses. Sonpavde et al. reported an analysis of 1445 patients at VA hospitals. They found no difference in overall survival among those who started with taxanes vs. those that started with a second-line hormonal therapy. In a study at Johns Hopkins, Maughan et al. reported that there were no statistically significant differences in total progression-free survival related to the order in which the medicines (Taxotere or Zytiga) were given. Both studies adjusted for disease characteristics.

In the STAMPEDE trial of newly diagnosed men with metastatic hormone-sensitive prostate cancer (mHSPC), there was no difference in survival among men who were randomized to get Taxotere or Zytiga first (see this link). The difference in the Mayo study may be due to "selection bias" in the retrospective study - Group A may have received Taxotere first *because* they were healthier, and more likely to survive.

But even if the survival difference is an artifact of the study methodology, there are other reasons to do Taxotere first:

- Side effects are less when chemo is given earlier
- In fact, side effects are no worse for chemo or Zytiga (see this link). The differences are in the kinds of side effects, but not in their seriousness.
- By starting with 6 infusions of Taxotere, one is able to use Zytiga after only 15 weeks; but if one starts with Zytiga, it may be 3 years before Taxotere can be tried (see this link).

There doesn't seem to be any cross-resistance between taxanes and Zytiga (as there is between Zytiga and Xtandi). A pilot trial combined the two without finding excessive toxicity, and larger trials of the combination are ongoing; for example, this one.

(2) Zytiga (abiraterone) before Xtandi (enzalutamide)

Khalaf et al reported the results of a randomized Phase 2 trial in British Columbia. 202 newly diagnosed mCRPC men were randomized to either Zytiga or Xtandi first. After progressing on the first therapy, they were given the second therapy (cross-over).

- The Zytiga-first men progressed after 19 months vs 15 months in the Xtandi-first group
- After cross-over, PSA was reduced by more than 30% in 36% of those who had Xtandi-second vs only in 4% of those who had Zytiga-second

Until we have a larger study that follows men for the rest of their lives, we can assume that the extended progression-free time among those who use Zytiga before Xtandi will translate to extended survival.

It's worth noting that it has been found that Zytiga can work a median of 10 months longer if one switches from prednisone (10 mg/day) to dexamethasone (0.5 mg/day) when progression begins (see this link).

A trial combining Zytiga and Xtandi found there was no benefit to combining the two drugs, but toxicity was worse than Xtandi alone. A small trial of Zytiga monotherapy (without ADT) showed that it can reduce testosterone on its own and another small trial suggested that oncological outcomes were not compromised by the monotherapy.

(3) Jevtana (cabazitaxel) third

Jevtana is currently FDA-approved for men in whom Taxotere has already been tried and failed. Jevtana and Taxotere (both taxanes) have been found to be virtually identical in oncological results when given as first-line therapy (see this link) with a similar degree of toxicity. If Taxotere and one of the second-line hormonal therapies (Zytiga or Xtandi) have already been tried, is it better to try the other second-line hormonal therapy next or is Jevtana a better choice for the third therapy? De Wit et al. found the answer.

They randomized patients who already had Taxotere and one of the two second-line hormonal to receive either the *other* second-line hormonal or Jevtana.

- 126 received Jevtana
- 58 received Zytiga
- 66 received Xtandi

After 9.2 months median follow-up,

- Imaging-based progression-free survival was 8.0 months for Jevtana vs 3.7 months for the hormonal therapy
- The advantage for Jevtana was maintained regardless of risk characteristics and treatment history
- The advantage for Jevtana was true regardless of which hormonal therapy it was compared to.
- Overall survival was 13.6 months for Jevtana vs 11.0 months for hormonals.
- PSA was reduced by at least 50% in 36% of men using Jevtana vs 14% using hormonals.
- Tumors shrank in 37% of men using Jevtana vs 12% using hormonals
- Serious adverse events of any grade were similar for all therapies at 39%.
- Adverse events leading to death were more frequent with the hormonals (11%) than Jevtana (6%)
- Pain was improved more by Jevtana (in 45% of men) than by hormonals (in 19% of men)
- Skeletal events (fractures, spinal compression) occurred more frequently among those taking hormonals (51%) than Jevtana (29%)

Jevtana was at least as good or had a clear advantage on every measure of success.

(4) Xtandi fourth

There is some evidence that taxanes (like Taxotere or Jevtana) can reverse one mode of hormonal resistance (AR-V7 splice variance). Research continues on methods to reverse resistance (e.g., see

subsection - "what's next?"). Although there is known cross-resistance between Zytiga and Xtandi, Xtandi usually works at least for a while after Zytiga.

Other medicines

Other medicines approved for men with mCRPC include older anti-androgens (like bicalutamide), Xofigo, Provenge, and Keytruda (but only in the rare event of MSI-hi/dMMR). It would save time if any of these could safely be piggybacked on top of another therapy.

Older anti-androgens (like Casodex or flutamide) are still used sometimes in the mCRPC setting, mostly in combination with a GnRH agonist (like Lupron). The combination is somewhat more beneficial (see this link) than a GnRH agonist alone, and provides a short-term benefit at low cost. Sometimes, the cancer learns how to feed on the anti-androgen, and *removing* it leads to a reduction in PSA (called antiandrogen withdrawal syndrome). Newer antiandrogens (like Xtandi) don't seem to do this.

It is unknown where the newest antiandrogens fit into sequencing. Erleada and Nubeqa have been approved for other indications, but not yet for mCRPC. Others (like proxalutamide) haven't yet cleared the first hurdle.

Xofigo cannot be prescribed after any visceral metastases have been detected, although it *may* work well on the bone metastases nevertheless. It works better sooner rather than later, but a trial combining it with Zytiga was stopped early because of a high rate of skeletal events. Early results of a new trial combining Xofigo and Xtandi show that adding a bone-protective agent (Xgeva or Zometa) can ameliorate the problem.

Provenge may synergize with radiotherapies or chemo because they present many cancer antigens for the amped up immune system to tune into. There is evidence that an abscopal effect (systemic immune response) may be augmented. Other immunotherapies, which show little therapeutic promise alone, *may* be beneficial in combination with chemo or other therapies.

PARP inhibitors are in clinical trials, and seem to be especially effective when there are BRCA1/2 mutations (germline or somatic). Several clinical trials are combing carboplatin with taxanes. Transdermal estrogen is inexpensive and is available now. Optimal sequencing or combinations are yet to be determined.

Lu-177-PSMA-617 and similar radiopharmaceuticals are in ongoing trials. The VISION trial used it only among men who had been pre-treated with chemo and Zytiga or Xtandi. If it gets FDA approval, it will be limited to use after those other treatments. However, trials are ongoing for earlier use and in combination therapy. There is probably an optimum time for use of PSMA-directed therapies. Combination with different PSMA-targeted radionuclides (like Ac-225), and with multiple membrane targets are being explored.

There are myriad other potential therapies in clinical trials. Many are pathway growth inhibitors that may work best in combinations. Therapies tailored to specific genomic mutations are in their infancy.