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Positive Quality Intervention: Darolutamide (Nubeqa) in combination with Docetaxel (Taxotere) for Metastatic Hormone Sensitive Prostate Cancer

Description: This PQI aims to provide information on the administration and management of adverse events, patient follow-up, and recommended dose reductions for darolutamide in combination with docetaxel for metastatic hormone sensitive prostate cancer (mHSPC).

Background: Darolutamide is an androgen receptor inhibitor. In preclinical studies, darolutamide does not appear to cross the blood-brain barrier, resulting in decreased neurological side effects, including seizures, which can be seen with other medications in this class.[1] Docetaxel is a microtubule inhibitor. Darolutamide is indicated in combination with docetaxel for men with metastatic hormone-sensitive prostate cancer. The patient received 6 cycles of docetaxel, starting within 6 weeks of initiating darolutamide. Androgen deprivation therapy (ADT) should also be initiated within 12 weeks of starting therapy unless the individual has undergone bilateral orchiectomy.[1] Median overall survival in the darolutamide plus docetaxel plus ADT arm has not yet been reached, but showed a 32% reduced risk of death, while docetaxel-plus-placebo arm was 48.9 month median overall survival (HR=0.68, 95% confidence interval [CI], 0.57-0.80). Time to disease progression 64% risk reduction compared to the control arm. Treatment with darolutamide and docetaxel resulted in a statistically significant delay in time to pain progression with time not yet being reached vs. 27.5 months respectively (HR = 0.79, 95% CI = 0.66–0.95). It was also noted that the addition of darolutamide does not significantly increase toxicity when added to ADT and docetaxel.[2] Darolutamide is a generally well-tolerated drug. Serious Grade 3/4 adverse effects have an incidence of less than 1% in patients treated with darolutamide plus ADT alone but this doubles with the addition of docetaxel.[1] It is important to distinguish chemotherapy side effects from darolutamide side effects and make appropriate dose modifications. NCCN has designated darolutamide plus docetaxel plus ADT as category 1 preferred regimen in mHSPC.[3]

PQI Process:[4]

- Start ADT within 12 weeks before administering darolutamide and docetaxel
- Initiate darolutamide at 600 mg twice daily with food
    - For patients with severe renal impairment (eGFR 15-29 mL/min) the recommended dose is 300 mg BID
    - For patients with moderate hepatic impairment (Child-Pugh class B) recommended dose is 300 mg BID
- Start docetaxel IV 75mg/m^2 every 3 weeks for 6 cycles within 6 weeks of initiating darolutamide

Darolutamide dose management[1]

- Treatment with darolutamide can be continued until disease progression/or unacceptable toxicity even if a dose of docetaxel is delayed, interrupted, or discontinued
- For sever renal impairment not receiving hemodialysis (GFR 15-29 mL/min/1.73 m^2) reduce dose to 300 mg BID
- Hold darolutamide or dose reduce to 300 mg BID for grade 3 adverse reaction; may be resumed at 600 mg twice per day once the adverse reaction returns to baseline
- Doses under 300 mg twice a day are not recommended

Permanently discontinue darolutamide in the event of

- Grade 3-4 ischemic heart disease
- Development of seizures during darolutamide therapy

Clinical pearls[1]

- Optimize cardiovascular risk factor management - hypertension, diabetes, dyslipidemia
- Use effective contraception during treatment and for 1week post last dose of darolutamide
- Avoid using darolutamide with a combined P-gp and strong or moderate CYP3A4 inhibitor/inducer
    - If combination is necessary, monitor patient more frequently
- Review prescribing information of the BCRP, OATP1B3, OATP 1B1 substrates when used concomitantly with darolutamide

Docetaxel dose management[4]

- Administer drug when ANC is at least 1500 cells/mm^3 or higher
- Dose reduce to 60 mg /m^2 if the patient experiences febrile neutropenia, ANC of <500 cells/mm^3 for more than 1 week, severe or cumulative skin toxicities, or moderate neurotoxicity
- If the patient continues to experience the above side effects at 60 mg/m^2 the treatment should be discontinued
- Grade 3 liver dysfunction- reduce docetaxel by 20%

Permanently discontinue docetaxel in the event of:

- Grade 4 liver dysfunction
- Severe hypersensitivity reaction to docetaxel

Clinical pearls[4-5]

- Monitor for fluid retention, and manage per institution guidelines
- Be aware of the irritant/vesicant potential of docetaxel and consider central line in patients with poor IV access
- Pre-medicate with oral dexamethasone 8 mg twice daily x 3 days, starting the day before docetaxel administration
- Consider prophylactic pegfilgrastim 24 hours post docetaxel due to risk for febrile neutropentia[6]

Patient-Centered Activities:

- Provide darolutamide Oral Chemotherapy Education Sheet and docetaxel Intravenous Cancer Treatment Education Sheet
- Side effects of combination therapy with darolutamide and docetaxel include neutropenia, neutropenic fevers, musculoskeletal pain, constipation, decreased appetite, rash, bleeding, weight gain, and hypertension
- Discuss risk for serious side effects including severe infusion reaction, development of seizures, and ischemic heart disease
- Ensure proper contraception and pregnancy protection is used and ensure the patient is aware that fertility may be impaired
- Provide education on temperature monitoring, whom to call if fever develops, and neutropenic precautions
- Recommend that patient immediately report any new or worsening symptoms
- Discuss the possible need for dose modifications of darolutamide, docetaxel, or both due to side effects
- Ensure the patient is aware of the use of steroids to prevent anaphylaxis and fluid retention associated with docetaxel

Reference:

1. Darolutamide prescribing information. Retrieved November 17, 2022.
2. Smith, M. H. (2022, (12)). Daralutamide and survival on metastatic hormone-sensitive prostate cancer. New England Journal of Medicine, pp. 1132-1142, DOI: 10.1056/nejmoa2119115.
3. National Comprehensive Cancer Network – Prostate Cancer. from https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.
4. Docetaxel prescribing information. Retrieved November 17, 2022.
5. Jamal, E. Z. (2018). Primary prophylactic GCSF in patients receiving docetaxol-based chemotherapy for breast cancer. Journal of Clinical Oncology, 136:15.