

6.5 Systemic treatments for prostate cancer

6.5.1 Hormonal therapy

Androgen deprivation can be achieved by suppressing the secretion of testicular androgens in different ways.

6.5.1.1 Castration level

The castration level of testosterone is < 50 ng/dL (1.7 nmol/L), defined more than 40 years ago when testosterone testing was less sensitive. Current methods have shown that the mean value after surgical castration is 15 ng/dL [1035]. Therefore, a more appropriate level should be defined as < 20 ng/dL (< 0.7 nmol/L). This definition is important as better results are repeatedly observed in ADT monotherapy cohorts with lower testosterone levels compared to 50 ng/dL [1036-1038]. However, the castrate level considered by the regulatory authorities and in clinical trials addressing castration in PCa is still the historical < 50 ng/dL (1.7 nmol/L).

6.5.1.2 Bilateral orchiectomy

Bilateral orchiectomy or subcapsular pulpectomy is still considered the primary treatment modality for ADT. It is a simple, cheap and low-complication procedure. It is easily performed under local anaesthesia, and it is the quickest way to achieve a castration level which is usually reached within less than twelve hours. It is irreversible and therefore does not allow for intermittent treatment [1039].

6.5.1.3 Luteinising-hormone-releasing hormone agonists

Long-acting LHRH agonists are currently the main forms of ADT. These synthetic analogues of LHRH are delivered as depot injections on a 1-, 3-, 6-monthly, or yearly basis. The first injection induces a transient rise in luteinising hormone (LH) and follicle-stimulating hormone (FSH) leading to the 'testosterone surge' or 'flare-up' phenomenon which starts two to three days after administration and lasts for about one week. This may lead to detrimental clinical effects (the clinical flare) such as increased bone pain, acute bladder outlet obstruction, obstructive renal failure, spinal cord compression, and cardiovascular death due to hypercoagulation status [1105]. Patients at risk are usually those with high-volume symptomatic bony disease. Concomitant therapy with an anti-androgen decreases the incidence of clinical flare but does not completely remove the risk. Anti-androgen therapy is usually continued for 4 weeks but neither the timing nor the duration of anti-androgen therapy are based on strong evidence. In addition, the long-term impact of preventing 'flare up' is unknown [1106].

Chronic exposure to LHRH agonists results in the down-regulation of LHRH-receptors, suppressing LH and FSH secretion and therefore testosterone production. A castration level is usually obtained within 2 to 4 weeks [1107]. Although there is no formal direct comparison between the various compounds, they are considered to be equally effective [1108]. So far, no survival difference between LHRH agonists and orchiectomy has been reported due to the lack of high-quality trials [1109]. The different products have practical differences that need to be considered in everyday practice, including the storage temperature, whether a drug is ready for immediate use or requires reconstitution, and whether a drug is given by subcutaneous or intramuscular injection.

6.5.1.4 Luteinising-hormone-releasing hormone antagonists

Luteinising-hormone-releasing hormone antagonists immediately bind to LHRH receptors, leading to a rapid decrease in LH, FSH and testosterone levels without any flare. The practical shortcoming of these compounds is the lack of a long-acting depot formulation with, so far, only monthly formulations being available. Degarelix is a LHRH antagonist. The standard dosage is 240 mg in the first month followed by monthly injections of 80 mg. Most patients achieve a castrate level at day three [1107]. A phase III RCT compared degarelix to monthly leuporelin following up patients for twelve months, suggesting a better PSA PFS for degarelix 240/80 mg compared to monthly leuporelin [1110]. A SR did not show a major difference between agonists and degarelix and highlighted the paucity of on-treatment data beyond twelve months as well as the lack of survival data [1111]. Its definitive superiority over the LHRH analogues remains to be proven. Short-term follow-up data from a meta-analysis indicate that the use of LHRH antagonist is associated with significantly lower overall mortality and cardiovascular events as compared with agonists. On the other hand, other adverse effects such as decreased libido, hot flushes, ED, weight gain, and injection site reactions are seen less often with the agonists [1112, 1113].

Relugolix is an oral LHRH antagonist. It was compared to the LHRH agonist leuprolide in a randomised phase III trial [1114]. The primary endpoint was sustained testosterone suppression to castrate levels through 48 weeks. There was a significant difference of 7.9 percentage points (95% CI: 4.1–11.8) showing non-inferiority and superiority of relugolix. The incidence of major adverse cardiovascular events was significantly lower with relugolix (prespecified safety analysis). Relugolix has been approved by the FDA [1115] and EMA [1116] for hormone sensitive PCa.