The future of Biploar androgen therapy

By Kalli Spencer

Metastatic prostate cancer is initially treated with androgen deprivation therapy (ADT) by inhibiting the cancer cells growth through blockade of testosterone (androgens). Despite a high initial response rate, most patients become castrate-resistant within 3 years from the start of treatment. As discussed in previous blogs castration resistance is not only due to ADT resistance. Despite the reduction of serum testosterone levels below 0,5 ng/mL, which defines castration-resistant prostate cancer (CRPC), there are mechanisms that are driven by the androgen receptor (AR) pathway.

Better understanding of these mechanisms led to the development of new generation hormonal therapies, such as enzalutamide and abiraterone. Enzalutamide is a more potent AR inhibitor compared to bicalutamide, that showed overall survival improvement for CRPC patients. Abiraterone acetate is a CYP17A1 inhibitor that potently blocks androgen synthesis in cancer cells, the testis and adrenal glands and showed similar efficacy against CRPC after ADT failure. However, despite the efficacy of these drugs, patient's outcomes have been affected by acquired resistance mechanisms. Studies have looked at initiating enzalutamide or abiraterone earlier in treatment, but this comes with a risk of higher clonal pressure that may lead to the development of alternative progression pathways (resistance) and to more aggressive disease that may not respond to subsequent treatments.

Bipolar androgen therapy (BAT) refers to an innovative therapeutic approach for metastatic prostate cancer (mPC) consisting of the combination of regular ADT with testosterone injections in order to reach supra-physiologic testosterone levels (higher than normal)[1]. This seems contrary to what has been previously written, but these super high levels of testosterone are thought to negatively affect the growth and spread of metastatic prostate cancer cells via cytostatic and cytotoxic pathways. It is thought to cause direct DNA damage resulting in cell death. The biological rationale for this therapy is to oppose the adaptive response of the cancer cells to ADT and maintain the cells in a prolonged hormone-sensitive state. The proposed mechanism is downregulation of AR expression.

During BAT there is rapid cycling between the extremes of supraphysiological and near-castrate serum testosterone concentrations in patients with metastatic castration-resistant prostate cancer after progression on enzalutamide. Evidence till now has shown a good clinical response but also that BAT may result in a transient resensitisation allowing for further enzalutamide therapy later[2]. This was shown in the RESTORE Trial where the study group found that BAT was more effective as a "resensitizer" than abiraterone[3].The TRANSFORMER Trial group showed that BAT was not superior to enzalutamide but demonstrated similar time to progression and prostate-specific antigen response following treatment with abiraterone[4]. They found that BAT can enhance the patient's quality of life (less fatigue, increased libido) with significant improvement in the magnitude and duration of response to enzalutamide.

Schweizer et al in their study published this year found that BAT plus an immunotherapy agent Olaparib (see previous blog) is associated with high response rates and long progression free survival (time taken before the disease progresses)[5]. Up until now immunotherapy has shown some benefit in those with a positive HRR gene mutation but this combination seems effective even in those without this mutation.

BAT has a reasonable safety and tolerability profile. This is a promising research area and future studies should focus on the best sequence of drug combinations to improve outcomes for patients with metastatic castration-resistant prostate cancer[2].

References

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Kalli has been involved with the Prostate Cancer Foundation of Australia for many years, advocating for improved cancer care and facilitating community prostate cancer support groups.