Conference Abstract

The role of chemohormonal therapy in metastatic hormone sensitive prostate cancer∗

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A R T I C L E I N F O

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1. Introduction

Androgen deprivation therapy (ADT) has been universally accepted as the initial treatment choice in advanced or metastatic prostate cancer. However, most patients invariably will progress on ADT and become resistant to castration, leading to poor outcomes and death. Recent new data presented on the earlier use of chemotherapy in addition to ADT, in the hormone sensitive metastatic prostate cancer setting, may potentially change management paradigms. However, the benefit of its efficacy needs to be balanced by judicious use in defined populations due to potential toxicities. Here, arguments for and against its use are presented.

2. Chemohormonal combination therapy should be used as first-line/upfront therapy in hormone sensitive M1 disease

Chemotherapy (intravenous docetaxel) was first approved for the treatment of metastatic castrate resistant prostate cancer (mCRPC) in 2004 after it showed improvement in survival and quality of life in this group of patients. Based on its efficacy in the mCRPC setting, chemohormonal therapy has recently been tested in the hormone sensitive setting. The rationale hypothesized was that this approach would deplete de-novo testosterone clones early, and would enable patients to receive chemotherapy before they experience a drop in performance status due to disease progression.

The first study to explore this was the GETUG-AFU 15 study which showed no overall survival benefit among patients who received chemohormonal combination or hormonal therapy alone.1 However the larger CHAARTED study showed a big improvement in overall survival (OS) (57.6 months vs 44.0 months, HR = 0.61, 95% CI 0.47–0.80).2 This improvement was seen particularly in a group of patients who were having high volume disease, which was defined as having visceral metastasis, or four or more bone metastases including one metastasis outside of the axial skeleton (HR = 0.60, 95%CI 0.45–0.81). The median OS improvement in this group was 17 months with the chemohormonal therapy.

The findings of CHAARTED were further supported by the STAMPEDE study results presented recently at ASCO 2015. In this multi-arm study (which included a subset of M0 patients), patients on the chemohormonal therapy arm had a longer overall survival (OS) benefit (77 months vs 66 months, HR = 0.76, 95%CI 0.63–0.91).3 A longer survival benefit of 22 months (65 months vs 43 months; HR=0.73, 95%CI 0.59–0.89) was seen in the subset of patients with metastatic disease. These data provide compelling evidence to support the use of chemohormonal combination as upfront therapy in metastatic hormone sensitive disease.

3. Chemohormonal combination therapy may not be the best first-line/upfront option for the treatment of hormone sensitive M1 disease

Chemotherapy using docetaxel has been accepted as one of the standard treatments for mCRPC patients. Recently, chemohormonal combination therapy has been suggested as first-line therapy in hormone sensitive metastatic prostate cancer patients (CHAARTED & STAMPEDE vs GETUG trials). Nevertheless, there is a need to re-evaluate its relevance, benefits and tolerability in daily practice within Asia, due to innate ethnic differences that could affect data applicability. In the CHAARTED trial, combination therapy improved OS compared to androgen deprivation therapy (ADT) alone.4 However, in the GETUG-AFU 15 trial, which was carried out in a similar patient group, there was no difference between the two groups (median OS: 58.9 vs 54.2 months; p = 0.955). It is also worth noting that, despite being a negative trial, the GETUG study allowed higher number of cycles of chemotherapy than CHAARTED (9 vs 6 cycles).
Higher incidence of serious adverse events after docetaxel chemotherapy have been reported in Asian patients and older patients. There are twice as many incidences of Grade 3 or 4 neutropaenia in the Asian study cohort than in the Caucasian group. Asian patients may also require lower doses of chemotherapy. In a multicenter retrospective review in Hong Kong, two in every five patients were given a non-standard dose. In addition, twenty percent of patients needed their initial dose modified because of haematological toxicities. Dose modifications are also needed for many elderly patients (age 80 years and older). Lastly, there is no outcome data supporting combination over sequencing of treatments in metastatic hormone-sensitive prostate cancer patients, such as the head-to-head comparison of first-line ADT followed by docetaxel vs first-line ADT with docetaxel. Therefore, chemotherapy may not yet be a viable option for first-line treatment in hormone sensitive metastatic prostate cancer patients in Asia. Asian patients have shown better response to hormonal manipulation than Caucasians. The use of ADT in hormone sensitive disease showed a relative response rate of 90%. There was also a significant OS benefit with combined androgen blockade with bicalutamide compared to luteinising hormone-releasing hormone monotherapy.

4. Conclusion

Strong evidence of efficacy in two large clinical trials has been presented, which is likely to drive the use of chemotherapy for hormone sensitive metastatic prostate cancer. However, there may be a need for newer biomarkers (including molecular markers) to better risk-stratify patients, in order to balance the benefits and risks of toxicity. Issues related to possible lower tolerability, access and cultural attitude to chemotherapy amongst Asian patients deserves further study.

Conflicts of interest

RK has received research support from Sanofi. He sits on the Scientific Advisory Boards for Astellas, Bayer, Janssen, Pfizer, Mundipharma.

YL did not declare any conflicts of interest.

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References