Mini Review

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Efficacy of Chemotherapy Combinations in Metastatic Castration-Resistant Prostate Cancer Patients - Do Homologous Recombination Deficiency Affect the Outcomes?

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Abstract

Homologous recombination (HR) is a major repair mechanism of DNA damage. Platin-based agents are known to be more effective in patients with impaired HR mechanism. Previous studies combined platin compounds with docetaxel, but most of these studies did not perform subgroup analysis for HR-deficient patients. Aggressive variant prostate cancer (AVPC) is considered more susceptible to carboplatin. Furthermore, prostate cancers with a higher rate of small cell or anaplastic carcinoma components are more susceptible to carboplatin plus etoposide. We thought that the effect of cabazitaxel plus carboplatin on the progression-free survival might be related to carboplatin alone. In a study that evaluated the effect of cabazitaxel plus carboplatin, the proportion of AVPC patients was higher in the combination group than in the cabazitaxel group. Additionally, the combination of cabazitaxel and carboplatin led to increased toxicity.
Keywords: Chemotherapy, homologous-recombination deficiency, prostate cancer

Several clinical trials investigated the efficacy of combination chemotherapy for metastatic castration-resistant prostate cancer (mCRPC). In most of these trials, combination regimens are not superior to single-agent regimen (e.g., docetaxel or cabazitaxel). Hence, docetaxel and cabazitaxel (especially in the second-line setting) are the standard chemotherapeutic agents for mCRPC (1,2).

Homologous recombination (HR) is a major repair mechanism of DNA damage. In a previous study, 20%-25% of CRPC patients had a defect in the HR repair genes (3). Particularly, BRCA2 mutations were more frequent than mutations of other HR repair genes (4,5). Platin-based agents are known to be more effective in patients with impaired HR mechanism. In previous studies, platin compounds were combined with docetaxel, but most of these studies did not perform subgroup analysis for patients with HR repair mechanism deficiency. However, a prospective analysis of mCRPC patients with BRCA2 mutations revealed the efficacy of docetaxel plus carboplatin (6).

Aggressive variant prostate cancer (AVPC) is defined based on the clinicopathological or molecular features of prostate cancer. Prostate cancer characterized by small cell or anaplastic carcinoma morphology and atypical features or mutations of *TP53*, *PTEN*, or *RB1* genes are considered as AVPC (7). Furthermore, BRCA mutation carriers have more aggressive prostate cancer (8). Therefore, mutations of BRCA and other DNA repair genes were seen commonly among patients with AVPC (9). Prostate cancers with these aspects are considered more susceptible to carboplatin (10). Furthermore, prostate cancers with a higher rate of small cell or anaplastic carcinoma components are more susceptible to carboplatin plus etoposide (11). In patients with mCRPC, *HR* gene defects (e.g., *PTEN* gene defect) cause aggressive prostate cancer and taxane resistance (12).

Corn et al. (13) showed that cabazitaxel plus carboplatin improved the survival outcome in patients with mCRPC. In this study, the effect of cabazitaxel plus carboplatin on the progression-free survival might be related to carboplatin alone. In this study, the proportion of patients with AVPC was also higher in the combination group than in the cabazitaxel group (the AVPC-clinicopathological criteria was 56% versus 52% and the AVPC-molecular signature was 52% versus 36% in the cabazitaxel and cabazitaxel plus carboplatin groups, respectively). Furthermore, the authors mentioned that the benefit from the combination therapy was greater in the AVPC group than in the non-AVPC group. Consequently, the results were consistent with the effect

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of carboplatin in AVPC. Additionally, combination of cabazitaxel and carboplatin led to increased toxicity in this trial.

To our knowledge, no clinical trial has compared the effect of carboplatin as a single agent with docetaxel or cabazitaxel among patients with *HR* gene mutations. An ongoing phase 2 trial compares the effectiveness of carboplatin and docetaxel among patients with BRCA1, BRCA2, or PALB2 mutations (NCT04038502). The results of this trial will clearly present the effect of carboplatin alone versus docetaxel among patients with who have *HR* gene mutations.

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