Am J Clin Exp Urol 2024;12(1):1-7
www.ajceu.us /ISSN:2330-1910/AJCEU0154684

Review Article

Neoadjuvant chemohormonal therapy before radical prostatectomy in high-risk prostate cancer: a mini-review

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Received November 29, 2023; Accepted January 31, 2024; Epub February 15, 2024; Published February 28, 2024

Abstract: High-risk localized prostate cancer (PCa) has the potential of recurrence and progression to a lethal phenotype, and neoadjuvant therapy followed by radical prostatectomy (RP) may be an option for these patients. Docetaxel has been recently shown to be an effective chemotherapeutic agent for high-volume metastatic hormone-sensitive PCa and metastatic castration-resistant PCa, and these increased efficacy create the impetus to assess the potential role of preoperative docetaxel in high-risk localized PCa. In this mini-review, we found that neoadjuvant chemohormonal therapy (NCHT) may be an effective neoadjuvant regimen to improve oncological outcome of high-risk PCa. However, the addition of docetaxel in the neoadjuvant setting would unavoidably increase the rate of adverse events, impose additional economic burdens. Therefore, suitable patient selection is crucial and pathological response might be a surrogate endpoint. Furthermore, we also found that molecular imaging prostate-specific membrane antigen (PSMA) PET/CT was a promising tool to evaluation the effectiveness of NCHT, and the expression status of AR, AR-V7, Ki-67, PTEN and TP53 might be helpful for urologists to identify more suitable candidates for NCHT.

Keywords: High-risk prostate cancer, neoadjuvant chemohormonal therapy, PSMA PET/CT, pathological response, predictive biomarkers, AR, AR-V7

Introduction

Prostate cancer (PCa) ranks as the second most common cancer among men worldwide and the sixth leading cause of cancer mortality worldwide [1]. Of all newly diagnosed PCa, approximately 15% present with high-risk localized PCa, and radical prostatectomy (RP) plus extended pelvic lymph node dissection is usually recommended to perform for these patients in clinical practice [2, 3]. However, most of patients with high-risk PCa will develop biochemical recurrence (BCR) following RP, and even after adjuvant therapy, up to 50% of patients will still develop BCR within 5 years [4, 5]. Thus, neoadjuvant systemic therapy may be an optimal option for these patients.

Docetaxel has been shown as an effective chemotherapeutic agent when combined with androgen deprivation therapy (ADT) not only for metastatic castration-resistant PCa, but also for high-volume metastatic hormone-sensitive PCa [6]. These increases of treatment efficacy create the impetus to assess the potential role of preoperative docetaxel in high-risk PCa. In this mini-review, we discuss the rational for neoadjuvant chemohormonal therapy (NCHT) and summarize the current knowledge regarding NCHT, with an emphasis on the use of neoadjuvant docetaxel. We also discuss the importance of a pathological response following NCHT, value of prostate-specific membrane antigen (PSMA) PET/CT and some novel biomarkers for predicting the effectiveness of NCHT.

The value of neoadjuvant chemohormonal therapy

Neoadjuvant treatment is defined as an induction therapy administered before local treat-

ment in order to reduce the local tumor burden and treat possible micrometastases. In the past few years, conventional ADT with or without next-generation androgen receptor signaling inhibitors (ARSIs) was the mostly used neoadjuvant regimen. However, the beneficial effects of neoadjuvant hormonal therapy (NHT) were only downstaging tumour stage and reducing positive surgical margins, while it did not translate to improve complete pathologic response rate or substantial survival benefits [7-9]. A potential explanation for this phenomenon is that castration-resistant cells are already present in the early stages of diseases, which has led to a renewed interest in adding chemotherapy to ADT in the neoadjuvant setting.

In a Phase II study that included 22 patients with high-risk PCa, neoadjuvant docetaxel and estramustine following RP were given, and the mean time to tumor recurrence was 23 (6-40) months and the mean 5-year disease-free survival at 53 months was nearly 80% for patients with ≤10% residual cancer [10]. Furthermore, this study also documented that NCHT was well tolerated, with only one grade 2 toxicity. Subsequently, another larger clinical trial was conducted by The Canadian Urologic Oncology Group (CUOG) to validate the feasibility of NCHT [11]. A total of 72 men with high-risk PCa were recruited and 64 patients completed the protocol. Of these patients, 3% patients (2/64) had a pathologic complete response and 25% patients (16/64) had ≤5% residual cancer in the radical prostatectomy (RP) specimen. After a median 42.7 months follow-up period, only 30% patients had prostate-specific antigen (PSA) recurrence.

A retrospective study performed by Pan *et al.* compared the outcome difference between NCHT, NHT and RP alone in patients with high-risk PCa [12]. 177 consecutive patients were included, and 60 patients in NCHT group, 73 patients in NHT group and 44 patients underwent RP alone. In terms of surgical outcome, there were no statistical differences in mean surgery time, mean blood loss, hospital stay and surgical complication. However, 42 patients (81%) in NCHT group achieved an undetectable PSA level after RP, which was significantly higher than NHT and RP alone. Furthermore, they also pointed out that NCHT had better biochemical progression-free survival (bPFS) time after RP compared to NHT or RP alone (P<0.001). Although more adverse events with those especially associated with chemotherapy were observed in the NCHT group than in the NHT group, the most of adverse events could be well tolerated and Grade 3 or 4 adverse events were relatively rare.

Nowadays, The Cancer and Leukemia Group B (CALGB) 90203 study was the only prospective randomized study to explore whether NCHT could improve bPFS over RP alone [13]. The overall rates of grade 3 and 4 adverse events were 26% and 19% for NCHT, respectively. The 3-year bPFS was 89% in NCHT group and no difference was seen between NCHT and RP alone (89% *vs.* 84%, P=0.11). However, NCHT was associated with improved overall bPFS, metastasis-free survival (MFS) and overall survival (OS) compared with RP alone. Therefore, NCHT might be an effective neoadjuvant regimen to improve outcome of patients with high-risk PCa. However, the addition of docetaxel in the neoadjuvant setting would unavoidably increase the rate of adverse events, impose additional economic burdens. To avoid these risks, patient selection is crucial.

Importance of the pathological response evaluation

The pathologic change revealed on the resection specimen was an important endpoint to evaluate in situ the effects of neoadjuvant therapies, and consequently to guide a personalized following therapy. An exploratory pooled analysis of three neoadjuvant studies showed that patients with pathological tumour downstaging or overall diameter of residual tumor <0.5 cm at final pathology developed no BCR during a 3-year follow-up period [14]. Subsequently, a pooled analysis of 117 patients with high-risk PCa treated with neoadjuvant ARSIs (34 patients received abiraterone; 17 patients received enzalutamide; 66 patients received both abiraterone and enzalutamide) showed that the 8% patients (2/25) with overall diameter of residual tumour <5 mm experienced BCR at a median follow-up period of 3.6 years, which was significantly better than patients with non-responders (diameter of residual tumour >5 mm) [15].

Nowadays, pathologic complete response (pCR) and minimum residual disease (MRD)

were the common pathologic surrogates to evaluate the efficacy of a neoadjuvant regimen in PCa. McKay *et al.* conducted a multicenter randomized Phase II trial to investigate the impact of intense androgen deprivation on radical prostatectomy pathologic response [16]. 118 patients were finally enrolled in this study and randomly assigned into APL group (abiraterone acetate, prednisone and leuprolide) and AAPL group (apalutamide, abiraterone acetate, prednisone and leuprolide), and the combined pCR or MRD rate was 22% in the AAPL group and 20% in the APL group, and no significant difference was observed (P=0.4). Recently, our recent study performed by Fan *et al.* retrospectively reviewed the data of 128 patients with primary high-risk localized PCa who had received NCHT followed by RP and found that 18 patients (14.1%) had a pCR and 77 (60.2%) patients experienced T downstaging [17]. However, pathologists might encounter several problems in assessing pCR and MRD in whole mount RP specimens in clinical practice as PCa was multifocal in ~60% of cases and had a high heterogeneity. Hence, an ideal definition of tumor response should incorporate the changes in tumor volume and cellularity. In addition, pretreatment biopsy cores should also be provided to reveal the baseline tumour cellularity.

To deal with these difficulties, Wang *et al.* firstly proposed a 5-tier (grades 0 to 4) histologic grading system for assessing NHT response [18]. They defined grades 0 to 1 as NHT resistant, and grades 2 to 4 as NHT sensitive. Using this grading system, 73% (62/85) patients in their study were belonged to NHT sensitive group and 27% (23/85) patients were belonged to NHT resistant group. The rate of organ confined diseases was 68% in NHT sensitive group and 30% in the NHT resistant group. Furthermore, no patients in NHT sensitive group had the pelvic lymph node metastases, but 4 patients (17%) in NHT resistant group had pelvic lymph node metastases [18]. Subsequently, in the study performed by Fan *et al.*, 75.78% patients (97/128) belonged to NCHT sensitive, who were had a high rate of T downstaging, negative surgical margin and undetectable PSA after RP [17]. Thus, this histologic grading system might be a promising tool to evaluate the pathologic response to neoadjuvant therapy in the future. However, the prognosis value of this grading system is still lacking. So, there are still need more multicenter studies to validate the value of this histologic grading system.

Role of PSMA PET/CT in NCHT

PSMA is a type II transmembrane protein highly expressed in PCa tissues, which is not only a cell-specific molecule, but also a disease progression biomarker [19-21]. In a single-centre, single-arm, Phase 1/2 Study, Eapen *et al.* demonstrated that up to two cycles of neoadjuvant [^{177}Lu] Lu-PSMA-617 in patients with high PSMA expression on PSMA PET/CT was safe and effective, delivering targeted doses of radiation to sites of tumor with high PSMA expression [22]. Thus, molecular imaging PSMA PET/CT is a possible way to assess disease in terms of oncogenic activity, treatment effectiveness and oncological outcome.

Shagera *et al.* retrospectively reviewed the data of 37 patients with metastatic PCa (mPCa) who both underwent ^{68}Ga-PSMA-11 PET/CT at baseline and after the last cycle of taxane-based chemotherapy (docetaxel or cabazitaxel), including 8 (22%) metastatic hormonal-sensitive PCa (mHSPC) and 29 (78%) metastatic castration-resistant PCa (mCRPC) [23]. PSMA responders (PSMA-R) were defined as a decrease of ≥30% of PSMA uptake after chemotherapy, and 18 patients (48.65%) were classified as PSMA-R, 19 patients were classified as PSMA non-responders (PSMA-NR). The PSMA-PET/CT response was concordant with PSA-response in 35 patients (100% in mHSPC and 85% in mCRPC). In addition, patients with PSMA-R had longer OS than patients with PSMA-NR (median OS not reached vs. 12 months, 95% CI: 0.03-0.39, *P*=0.01). The results from this retrospective study suggested that PSMA PET/CT was a promising tool to assessing response to taxane-based chemotherapy in mPCa.

In a retrospectively study conducted by Du *et al.*, 70 patients with high-risk, nonmetastatic PCa and underwent PSMA PET/CT before neoadjuvant therapy were included [24]. Among these patients, 36 (51.4%) patients had PSA persistence after RP, and the rate of PSA persistence was significantly higher among patients upstaged based on PSMA PET/CT than those not upstaged (65.8% vs. 44.0%, P=0.01). Moreover, the tumor stage based on PSMA-

PET/CT was significantly associated with PSA persistence (OR: 5.696, 95% CI: 1.293-25.089, *P*=0.02). Subsequently, in a prospective study, the clinicopathologic characteristic of 72 high-risk PCa patients who received NCHT followed by RP were reviewed, and pCR and MRD were defined as a favorable pathologic response to NCHT. Of these patients, 5 patients (6.94%) had pCR and 19 patients (26.39%) had MRD after NCHT. Furthermore, multivariate logistic analysis revealed that the post-NCHT maximum standardized uptake value (SUVmax) of the primary lesions on ^{68}Ga-PSMA PET/CT was an independent predictor of a favorable pathologic response to NCHT (OR=0.209, 95% CI: 0.102-0.429, *P*<0.001) [25].

Predictive biomarkers for NCHT

Earlier prediction of neoadjuvant treatment response might be beneficial for the adoption of novel therapeutic approaches and also identification of candidates who would get improved results from neoadjuvant treatment.

A study conducted by McKay *et al.* found that patients with PTEN loss, ERG positivity might be more easily resistant to neoadjuvant ADT+ ARSIs. Furthermore, glucocorticoid receptor, TP53 and AR-V7 were also predictive biomarkers of NHT efficacy [16]. Thus, patients with signatures of aggressive disease (TP53 mutations) or signatures of resistance against ARSIs (AR-V7) might benefit from the addition of chemotherapy early.

Testosterone plays a significant role in PCa, but the relationship between the serum testosterone level and the effectiveness of NCHT was still unclear. Eastnam *et al.* used the data from Alliance/CALGB 90203 to explore whether baseline testosterone level identified men at higher risk for progression after NCHT, and 324 patients with available baseline testosterone levels were finally included [26]. However, significant difference between baseline testosterone levels and OS or event free survival was not observed in this study.

We previously reviewed the data of 128 patients with primary high-risk localized PCa who had received NCHT followed by RP [17]. The pathologic response to NCHT in whole mount RP specimens was measured based on a 5-tier (grades 0 to 4) histologic grading system proposed by wang *et al.* [18], and patients with Grade 0-1 were categorized as having an unfavorable response, while others were categorized as having a favorable response. Ninety-seven patients (75.78%) had a favorable response to NCHT. Logistic regression showed that the preoperative PSA level, low AR expression and high Ki-67 expression in biopsy specimens were associated with a favorable pathologic response (*P*<0.05). Subgroup analysis revealed that the rate of favorable pathologic response to NCHT was 88.5% in patients with $AR^{low}Ki\text{-}67^{high}$, which was higher than patients with $AR^{low}Ki\text{-}67^{low}$, $AR^{high}Ki\text{-}67^{low}$ and $AR^{high}Ki\text{-}67^{high}$ (88.5% vs. 73.9%, 72.9% and 70.9%, all *P*<0.05). However, the expression status of PTEN, AR-V7, ERG was not associated with the pathologic response to NCHT, as the rates of PTEN negative, AR-V7 and ERG positive were as low as 15.63%, 10.90% and 14.06%, respectively.

Moreover, patients with mutations in homologous recombination genes (such as BRCA1, BRCA2 and ATM) might benefit from the addition of poly (ADP-ribose) polymerase (PARP) inhibitors in the neoadjuvant regimen [27] and patients with mutations in mismatch repair genes (for example, MSH 6, MSH 2) might benefit immunotherapy-based neoadjuvant treatment regimen [28]. In addition, patients with higher PSMA expression on PSMA PET/CT might benefit from neoadjuvant [^{177}Lu] Lu-PSMA-617 [22] (**Figure 1**).

Conclusion

NCHT might be an effective and safe neoadjuvant regimen for high-risk PCa, but the addition of docetaxel in the neoadjuvant setting would increase the rate of adverse events, impose additional economic burdens. Therefore, patient selection is crucial and pathologic response might a crucial evaluation endpoint. Moreover, the expression status of AR, AR-V7, Ki-67, PTEN, TP53 and PSMA PET/CT might be helpful for urologists to identify more suitable candidates for NCHT, and more biomarkers will be identified based on the new generation high-throughput sequencing, genetic testing and liquid biopsy.

Acknowledgements

The authors appreciate Prof. Xinyang Wang and Prof. Liang Liang from the Department of Urology, the First Affiliated Hospital of Xi'an

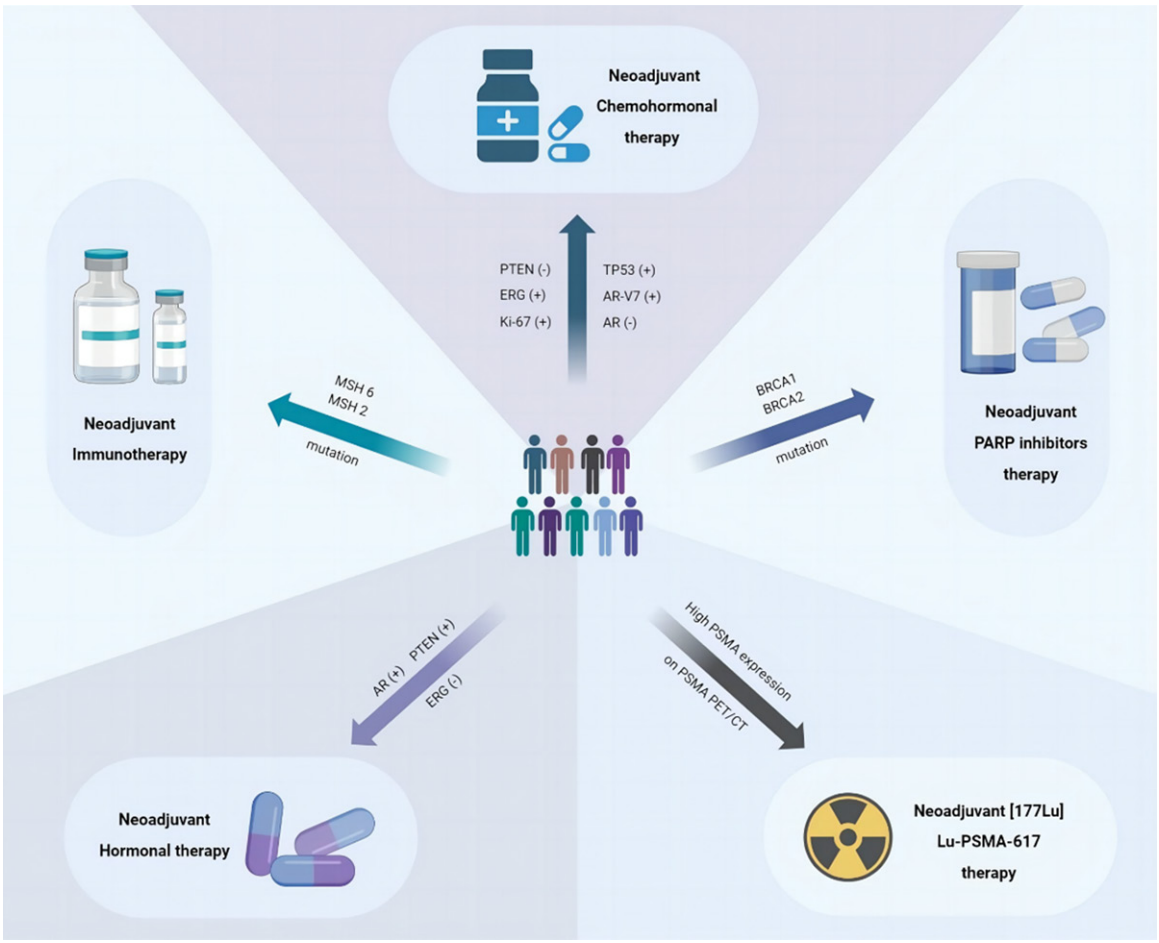

Figure 1. Predictive biomarkers for selection of different neoadjuvant treatment regimen.

Jiaotong University for helping with this paper. This study was supported by the National Natural Science Foundation of China (NSFC 81202014 to KW), New-Star Young Scientists Programme in Shaanxi Province (2017KJXX-35 to KW), the Fundamental Research Funds for the Central Universities (to KW) and the Natural Science Foundation in Shaanxi Province (2023-JC-QN-0890 to JJF).

Disclosure of conflict of interest

None.

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