Case Report

Neoadjuvant chemotherapy for high-risk prostatic adenocarcinoma

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Abbreviations & Acronyms
3T mpMRI = 3 Tesla multiparametric MRI
ADT = androgen-deprivation therapy
EBRT = external beam radiation therapy
ECE = extracapsular extension
MCRPC = metastatic castrate-resistant prostate cancer
MRI = magnetic resonance imaging
PI-RADS v.2 = Prostate Imaging Reporting and Data System version 2
PSA = prostate-specific antigen

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Received 31 July 2018; accepted 3 November 2018. Online publication 28 January 2019

Introduction: Neoadjuvant chemotherapy in high-risk, locally advanced prostate cancer remains an understudied area of prostate cancer. Chemotherapy continues to be a viable option. The combination with surgery may be desired but lacks data for complete recommendation.
Case presentation: We demonstrate the successful utilization of chemotherapy in the neoadjuvant arena. A 70-year-old male was diagnosed with high-risk prostate cancer on biopsy. Upon multiparametric magnetic resonance imaging, the patient had local rectal wall invasion and stage T4 N0 M0 after a negative bone scan. After treatment with androgen-deprivation therapy and docetaxel, repeat multiparametric magnetic resonance imaging showed regression of rectal invasion. The patient elected for prostatectomy and avoided proctectomy and colostomy. The patient's postoperative prostate-specific antigen was undetectable on initial follow-up.
Conclusion: We show that neoadjuvant chemotherapy merits further study and may provide a more permanent surgical option for patients.

Key words: docetaxel, neoadjuvant chemotherapy, prostate cancer, prostatectomy, prostatic adenocarcinoma.

Keynote message

This report indicates a possible advancement in how chemotherapy can be used to treat prostate cancer in the future. While this report does not offer any data on the overall effectiveness of docetaxel therapy on prostatic adenocarcinoma in the aggregate, it can be viewed as further support for continued exploration of neoadjuvant therapy.

Introduction

Prostate cancer is the second most common cancer in men worldwide. Although some prostate cancers present a low risk of metastasis, those in the high-risk category present urologists with difficult decisions. Recent studies have demonstrated the effectiveness of chemotherapy combined with ADT as a viable option along with radiotherapy or surgery. The combination of neoadjuvant chemotherapy and surgery, however, remains under-investigated. Patients may desire surgical resection but would often require neoadjuvant therapy to make surgery possible. We present the case of successful neoadjuvant chemotherapy for a high-risk, locally advanced prostate cancer patient to demonstrate the promise of this emerging management option.

Case presentation

We present a 70-year-old male with a history of elevated PSA of 23.4. The Eastern Cooperative Oncology Group performance status was 0. A right-sided nodule and fixed rectal wall were noted on digital rectal examination. The patient was scheduled for 3T mpMRI of the prostate. This revealed a PI-RADS v.2 5 lesion involving the posterior prostate with evidence of ECE and rectal wall invasion (Fig. 1).[1] A second PI-RADS 4 lesion was noted within the

left anterior mid-gland. There was no evidence of pelvic nodal metastasis. Subsequent ultrasound-guided biopsy (Fig. 2) revealed Gleason 4 + 4 = 8 adenocarcinoma (in 13 of 18 biopsies), Gleason 4 + 3 = 7 adenocarcinoma (in 4 of 18 biopsies), and Gleason 3 + 3 = 6 adenocarcinoma (in 1 of 18 biopsies). Bone scan was negative and the patient's clinical stage was T4 N0 M0.

Management options were discussed at a multidisciplinary tumor board. Given the local extension of disease, surgery was tabled and the patient was scheduled for consultation with medical and radiation oncology. Considering the results of the STAMPEDE trial, he was offered ADT with leuprolide plus docetaxel with plans for restaging after three cycles.[2] He received docetaxel 75 mg/m^2 IV every 21 days and Lupron 22.5 mg IM every 3 months. Following his third round of treatment, he underwent repeat 3T. This demonstrated resolution of rectal invasion (Fig. 1).

Due to therapeutic improvement, he was offered surgery and EBRT. Following counseling, including risks of proctectomy and colostomy, the patient chose open radical prostatectomy with extended bilateral pelvic lymph node dissection. Intraoperatively there was mild reaction noted posteriorly with soft and edematous tissue planes. The prostate was dissected in standard retrograde fashion (starting with apical dissection and opening the Denonvillier's fascia to the seminal vesicles). The prostate and neurovascular bundles were bilaterally peeled off the rectal serosa easily. The tissues were slightly edematous making planes well defined. After blunt and sharp dissection, the rectum was inspected closely. The serosa was intact and without evidence of rectal damage. There were no gross abnormalities or evidence of prostatic invasion. Extended lymph node dissection was completed and all nodes were clinically negative. No post-chemotherapy scarring of the perilymphatic or perivascular areas was noted. The patient was admitted to the floor postoperatively and discharged after 36 h.

Ten days postoperatively, he presented for catheter removal and pathology review which demonstrated acinar type adenocarcinoma involving 34% of the prostate with extensive right posterior ECE, negative margins, and seminal vesicle invasion. A single 3-mm metastatic deposit was present in the left external iliac nodal chain (Fig. 2). Gleason grade could not be assigned secondary to chemotherapeutic effects on the tissues (Fig. 2). 1 and 4 months postoperatively, serum PSA value remains undetectable (<0.1 ng/dL). Final pathologic stage was ypT3b ypN1 M0. Pathologists had difficulty grading the cancer as there were significant post-chemotherapy changes like diffuse scarring and loss of normal architecture.

Discussion

We present this case to stimulate conversation around neoadjuvant chemotherapy for high-risk, clinically nonmetastatic patients. As improvements in prostate cancer care continue, we must remember where we have come, and where we are headed. The past 15 years have been a renaissance in treatment. Initially, the focus was post-docetaxel MCRPC.[3,4] Improvements in survival with agents like enzalutamide and abiraterone led to studies on MCRPC without prior docetaxel,[5,6] then to hormone-sensitive metastatic disease with the release of the STAMPEDE,[2] CHAARTED,[7] and the LATITUDE[8] trials. The non-MCRPC space was highlighted with the approval of apalutamide following the phase III

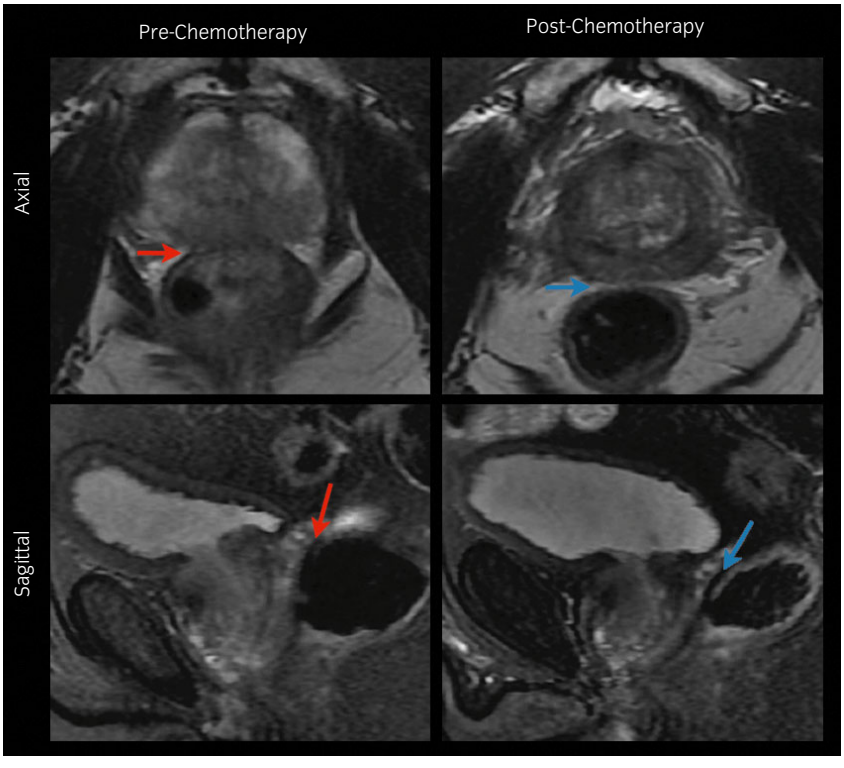

Fig. 1 T2-weighted mpMRI completed before and after chemotherapy. Using bony landmarks, pre- and post-chemotherapy images were appropriately aligned. Red arrows denote loss of fat plane between the prostate and the rectum consistent with rectal wall invasion. Blue arrows denote restoration of fat plane between the prostate and rectum following chemotherapy.

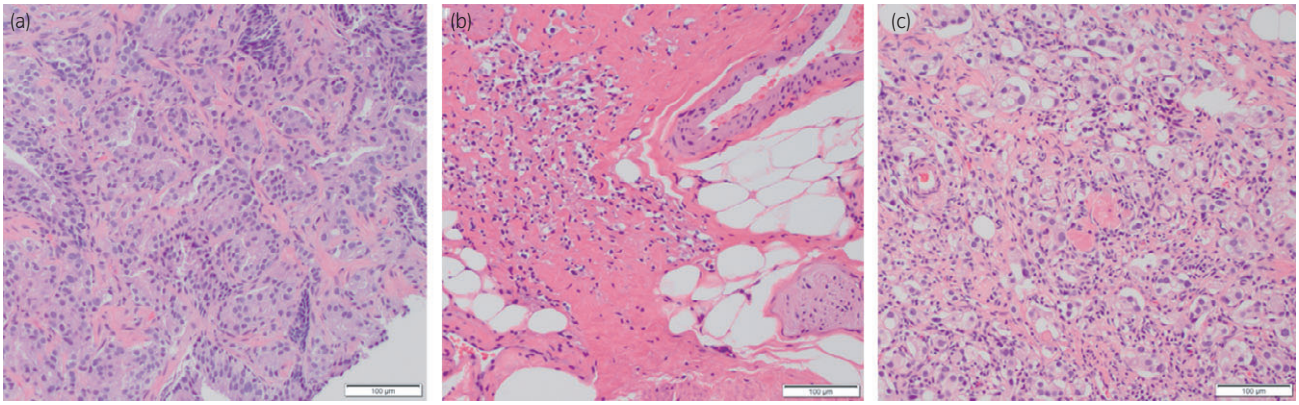

Fig. 2 (a) Pretreatment prostate biopsy core demonstrating Gleason 4 + 4 = 8 adenocarcinoma. Demonstrates acinar type adenocarcinoma with poorly formed glands, prominent nucleoli and abundant foamy pink cytoplasm. (b) Radical prostatectomy specimen showing chemotherapeutic effects on the tissue and extracapsular extension. Note the tumor cells now have a shrunken appearance with smaller darkened nuclei and clear more scanty cytoplasm. (c) Focus of prostatic adenocarcinoma within a pelvic lymph node. Note that all images were taken at 10× power. Scale of 100 μm provided in the lower right corner of each image.

SPARTAN trial.[9] We suspect enzalutamide will soon be granted approval for this same population with the PROSPER trial.[10]

Regarding our patient (clinically nonmetastatic, hormone-naïve, high-risk), the STAMPEDE trial demonstrated that upfront abiraterone or docetaxel outperformed ADT alone when looking at cancer-specific and failure-free survival.[2] This trial mandated EBRT for nonmetastatic patients but did not offer surgery; therefore, the investigators found no association between the use of EBRT and survival. Thus, how to manage surgical therapy in this scenario remains understudied. The question that remains is when the high-risk, clinically nonmetastatic patient elects surgery, should he receive neoadjuvant chemotherapy?

Several phase II trials have investigated this but a paucity of phase III trials in this arena remains.[11] A couple of phase III trials in this space are ongoing. The Alliance for Clinical Trials in Oncology Trial (NCT00430183) is combining surgery with and without docetaxel plus ADT in high-risk patients. Seven hundred and eighty-eight patients have enrolled since 2006; results are expected soon.[11,12] The ARNEO trial (NCT03080116) is not yet recruiting but will combine degarelix with or without apalutamide followed by radical prostatectomy.[13]

We continue to explore chemotherapy in different prostate cancer populations. Recently, several agents have proven useful over a range of patients. It remains to be seen whether adjuvant or neoadjuvant abiraterone, enzalutamide, apalutamide, or docetaxel improve outcomes when used alongside surgery. We present this case to promote dialog about potential use of these agents in clinically nonmetastatic, high-risk patients. In our patient, we feel neoadjuvant docetaxel allowed us to proceed to surgery without need for proctectomy with colostomy. Although ADT likely contributed to regression of the tumor, the success of ADT and docetaxel seen in prior phase II trials may merit its use in the neo-adjuvant space. Also, we have a short follow up with only 4 months of postoperative PSA trend which itself can be affected by Lupron. Whether this approach translates to improved PSA recurrence-free survival, metastasis-free survival, or cancer-specific survival is unknown. Nonetheless, we demonstrate its ability to provide a realistic surgical option by reducing risk of complications like colostomy. We hope that exploration of new avenues for prostate cancer treatment proceeds and that continued research in the nonmetastatic, high-risk patient remains ongoing.

Conflict of interest

The authors declare no conflict of interest.

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