Successful treatment with an anti-PD-1 antibody for progressing brain metastases in renal cell cancer

We present the case of a woman age 54 with clear-cell renal cell cancer (ccRCC), who developed metastases in multiple organs including one brain metastasis (gyrus cinguli). She was treated with pazopanib and the solitary brain metastasis was irradiated with 30 Gy in July 2013. In February 2014, after 8-month treatment with pazopanib, this metastasis increased in size and two new brain metastases were detected. Whole brain radiotherapy was performed leading to a cumulative dose of 52.5 Gy at the site of the gyrus cinguli metastasis.

The patient was subsequently treated with bevacizumab for progressive cerebral oedema interpreted as radiation-induced brain necrosis. Upon systemic and central nervous system (CNS) progression 5 months later (Figure 1A), treatment with axitinib was started—achieving partial response (PR) (Figure 1B). However, after 4 months, in March 2015, further systemic and CNS progression was documented (Figure 1C).

Treatment with pembrolizumab, a novel human programmed death receptor-1 (PD-1)-blocking antibody, was initiated. Pembrolizumab was chosen due to off-label availability at a time when no anti-PD-1 or anti-PD-ligand (L)1 antibody was licensed in Europe. After four infusions, the patient experienced complete resolution of lung metastases, stabilization of other metastases. Importantly, regression of all brain metastases was documented on magnetic resonance imaging (Figure 1D). This excellent response was seen despite continued steroid use of 4 mg dexamethasone/day and is still ongoing after 7 months of treatment (Figure 1E).

There are data on the safety and limited efficacy of sunitinib [1] and other vascular endothelial growth factor targeted therapies [2] in ccRCC patients with active brain metastases. New checkpoint inhibitors are currently under investigation for ccRCC and have shown promising results with improvement of overall survival for patients treated with the anti-PD-1 antibody nivolumab compared with everolimus; however, metastasis to the CNS was a key exclusion criterion in the CheckMate 025 study [3]. No data are published on the effect of anti-PD-1 or anti-PD-L1 antibodies on progressing brain metastases requiring systemic steroids. In early clinical trials with new checkpoint blocking agents, only patients with no or treated and stable brain metastases were eligible [4, 5].

In a phase II trial, the anti-cytotoxic T-lymphocyte-associated protein-4 antibody ipilimumab was assessed in melanoma patients with brain metastases. This study also included 21 patients receiving systemic steroids due to symptomatic brain metastases. Out of these, one patient showed a PR at week 12, all other patients progressed.

Figure 1. (A) MRI images at progression on bevacizumab. (B) PR on axitinib. (C) Before pembrolizumab. (D) Response to pembrolizumab after 4 months. (E) Ongoing response to pembrolizumab after 7 months.
For the anti-PD-L1 antibody MPDL3280A, there is concern that patients with untreated brain metastases may develop increased inflammatory infiltrate and vasogenic oedema. There is one report of a patient developing seizures after MPDL3280A treatment. Patients with active brain metastases are therefore currently excluded from trials with this compound. In our patient, CNS oedema decreased under pembrolizumab, but given in combination with steroids.

Tumour responses typically continue even after a course of steroids for treatment of adverse events [6], a fact that disputes given in combination with steroids.

Our observation should initiate formal evaluation of novel checkpoint inhibitors also in patients on systemic steroids, therefore not excluding them any longer from potentially very effective treatments.

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References


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Many men with castrate-sensitive metastatic prostate cancer should not receive chemotherapy

We wish to express our concern and disagreement with the (grade 1A) recommendation in the ESMO clinical practice guidelines for prostate cancer [1] that: ‘androgen deprivation therapy (ADT) plus docetaxel is recommended as first-line treatment of metastatic, hormone-naïve disease in men fit enough for chemotherapy’.

The results of the GETUG-15 [2], CHAARTED [3] and (as yet unpublished) STAMPEDE trials [4] are important and should lead to change in practice for fit patients presenting with high-volume metastatic prostate cancer, but the guideline fails to recognize that metastatic prostate cancer is an extremely heterogeneous disease. In all three trials, at least 70% of the participants presented with de novo metastatic disease, and their results do not give useful information about men with low-volume disease, or those who develop metastatic disease some years after diagnosis of localized prostate cancer. Such men present commonly in oncologic practice, and including them in this guideline has the potential to lead to substantial harm with minimal evidence of benefit.

The authors state as justification: ‘the effect size (in the CHAARTED trial) was consistent across all subgroups. For example, the HR for overall survival was 0.63 (0.45–0.81) for men with high-volume disease, and 0.63 (0.34–1.17) for those with low-volume disease’ [1]. However, there are at least four reasons not to extend the guideline to men with low-volume disease or to those presenting with metastases at a long time after diagnosis of the primary.

(i) Such patients represent a small subset in each of these three trials.
(ii) Relapse and death after standard ADT are delayed in such patients so that they contribute few events (note the wide confidence interval and nonsignificant result for such men in the CHAARTED trial).
(iii) Consistency of results is important when generating a guideline and although CHAARTED and STAMPEDE appear to be consistent for men with high-volume disease, there is no consistent information about men with low-volume disease. Also, there were ‘apparently’ few men in the metastatic cohort of the STAMPEDE trial who did not present de novo with metastatic disease—we use ‘apparently’ because the results of this trial are not yet published and we (and the authors of the guideline) are relying on abstracts presented at meetings.
(iv) Docetaxel has toxicity, with occasional mortality. There is evidence from its use to treat castration-resistant prostate cancer that median survival when used in unselected nontrial patients is much lower than that for selected trial patients and toxicity is much greater [5]. We can expect the same from its use to treat castrate-sensitive disease, and widespread application of the above recommendation to men with slowly progressive and/or low-volume disease, who may have prolonged response to ADT alone, could lead to substantial harm.

We urge the authors of the guideline to issue an addendum, limiting their recommendation for use of docetaxel and ADT to fit men with high-volume disease and those presenting de novo with metastases.