Nivolumab–ipilimumab in renal cell carcinoma metastatic to the bones: A case report

Marilena Di Napoli

Department of Urogynecology, National Cancer Institute, Pascale Foundation (Scientific Institute for Research and Healthcare), Naples, Italy

Abstract. In recent years, the introduction in the clinical setting of treatment combinations having immune checkpoint inhibitors as the backbone has dramatically improved the outcomes of patients suffering from advanced/metastatic renal cell carcinoma (RCC). Here we report the clinical course of a patient with a rapid and bulky bone recurrence of RCC after nephrectomy, experiencing a long-term benefit from the nivolumab–ipilimumab combination administered as first-line treatment.

Keywords: RCC; bone metastases; radiotherapy; PD-1; CTLA-4; immunotherapy

Introduction

The treatment landscape of advanced/metastatic renal cell carcinoma (RCC) has recently been revolutionized by the major clinical benefit achieved with immune checkpoint inhibitors (ICI) directed against the programmed cell death protein 1 (PD1). After their approval in the second-line treatment setting of advanced RCC [1], several strategies have been evaluated in the first-line treatment scenario. In comparative clinical trials, PD-1 inhibitors have been proved superior to the well-established first-line treatment sunitinib, in combination either with anti-angiogenic agents (e.g. cabozantinib–nivolumab, lenvatinib–pembrolizumab, axitinib–pembrolizumab) [2-4] or, specifically for nivolumab, with ipilimumab, an ICI directed against the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) [5]. These results prompted the introduction of the associations mentioned above in the upfront treatment of metastatic, clear cell RCC (ccRCC).

According to the latest update of the European Society for Medical Oncology (ESMO) guidelines, the mentioned combinations of ICI directed against PD-1 and anti-angiogenic agents and of nivolumab–ipilimumab are recommended regardless of the International Metastatic RCC Database Consortium (IMDC) risk group and in the intermediate- and poor-risk IMDC groups, respectively [6]. In the 2020 guidelines of the Italian Association of Medical Oncology (AIOM) (that recapitulate the segregation into IMDC risk groups mentioned above), pembrolizumab–axitinib was the only ICI/anti-angiogenesis combination recommended [7]. Nivolumab–ipilimumab was endorsed as well, waiting for the approval from the local drug agency, which was eventually obtained at the beginning of 2022.

Here we report the favorable outcomes in a patient suffering from the bone-exclusive recurrence of a previously resected ccRCC. After palliative radiotherapy to the largest lesion in the pelvis, a rapid and long-lasting clinical benefit with the nivolumab–ipilimumab combination was achieved.

Case presentation

In October 2018, a 45-year-old man, with no relevant medical history, no cases of malignant diseases in the family and no tobacco exposure, underwent a renal echography after the onset of hematuria in the previous two months. The exam revealed a mass in the right kidney, highly evocative for a neoplastic lesion. After

negative radiological staging, the patient underwent radical right nephrectomy. Histological examination revealed a ccRCC, pT3NxMx.

The patient underwent a clinico-radiological follow-up until May 2019, when a bone scintigraphy revealed an abnormal uptake at the left acetabulum, causing pain of the ipsilateral leg. The subsequent total-body CT scan confirmed the appearance of a wide bone lesion (125x120 mm) tearing apart the bone structures of the left ilium and invading the adjacent soft tissues, without affecting iliac vessels or peritoneal structures. After the histological confirmation of a bone metastasis from a ccRCC, the patient underwent palliative radiotherapy (30 Gy administered in 10 fractions of 300 cGy each). Given the pain control obtained with radiotherapy and the absence of additional localizations of metastatic disease, after the tapering of the steroid therapy, a wait-and-see approach was preferred. Forty days after the conclusion of radiotherapy, a novel CT scan documented a mild volumetric increase of the known lesion with infiltration of the adjacent muscles (Figure 1A), and the presence of a novel lesion in the posterior segment of the ninth right rib, evoking an additional metastatic site, while no parenchymal lesion was detected.

Taking into consideration the progression after a short timeframe following the radiotherapy and the notion that the iliac lesion was not under control, no additional local treatment was envisaged, and the patient was selected for a first-line systemic treatment. Despite the good clinical conditions (ECOG performance status: 0), the patient presented an intermediate IMDC risk. Given the lack of reimbursement of the nivolumab-ipilimumab combination at the time of treatment initiation, the benefit in terms of survival observed in the CheckMate 214 clinical trial fostered the administration of the drug combination mentioned above in the setting of the Italian Expanded Access Program. After four cycles of the combination therapy, a CT scan documented a reduction of both the bone lesions (the dimensions of the left ilium lesion decreased from 120 mm to 80 mm), compatible with a partial response according to the Response Evaluation Criteria in Solid Tumours (RECIST) criteria, without the appearance of any new disease localization. Having completed the four courses of ipilimumab, nivolumab was maintained, consistently with the treatment schedule. No adverse event was reported. The patient suspended the nivolumab treatment temporarily (in the period January-March 2021) because of the concomitant diagnosis of COVID-19 (with mild symptoms, not requiring hospitalization) (see the aspect of the ilium lesion in Figure 1B). Nivolumab was then reintroduced and its administration is still ongoing, with disease control confirmed at the latest CT scan in October 2021, two years after the treatment initiation (Figure 1C). Nivolumab administration will be maintained until disease progression or the onset of relevant toxicities.

Discussion

Novel treatment paradigms incorporating ICI have dramatically improved the survival outcomes for patients suffering from advanced/metastatic RCC. With particular regard to the anti-PD-1/anti-CTLA-4 combination in the first-line setting, the results of the CheckMate 214 trial (nivolumab–ipilimumab *vs.* sunitinib) have been updated with an extended follow-up. The four-year progression-free survival (PFS) probability was 31% in the experimental arm, compared to 17.3% in the sunitinib arm [7]. In patients belonging to the intermediate/poor risk IMDC group, overall survival rates at four years were 50% and 35.8%, respectively [8]. Conditional survivals, a measure to predict outcomes at landmark time-points, have been reported at ESMO 2021 congress. In the nivolumab–ipilimumab arm, the probability of remaining alive two years beyond the three-year landmark (conditional overall survival, cOS) was 81% and 79% in the global and intermediate/poor risk IMDC group populations, respectively, highlighting the long-term benefit derived from the combination treatment [9]. Taken together, these data strongly support the recent approval and reimbursement of nivolumab–ipilimumab for the first line treatment of advanced/metastatic RCC by the Italian drug agency.

In the clinical case we described here, the disease recurred after a short period following the radical nephrectomy (about seven months) with a bulky bone lesion, controlled with radiotherapy for a limited

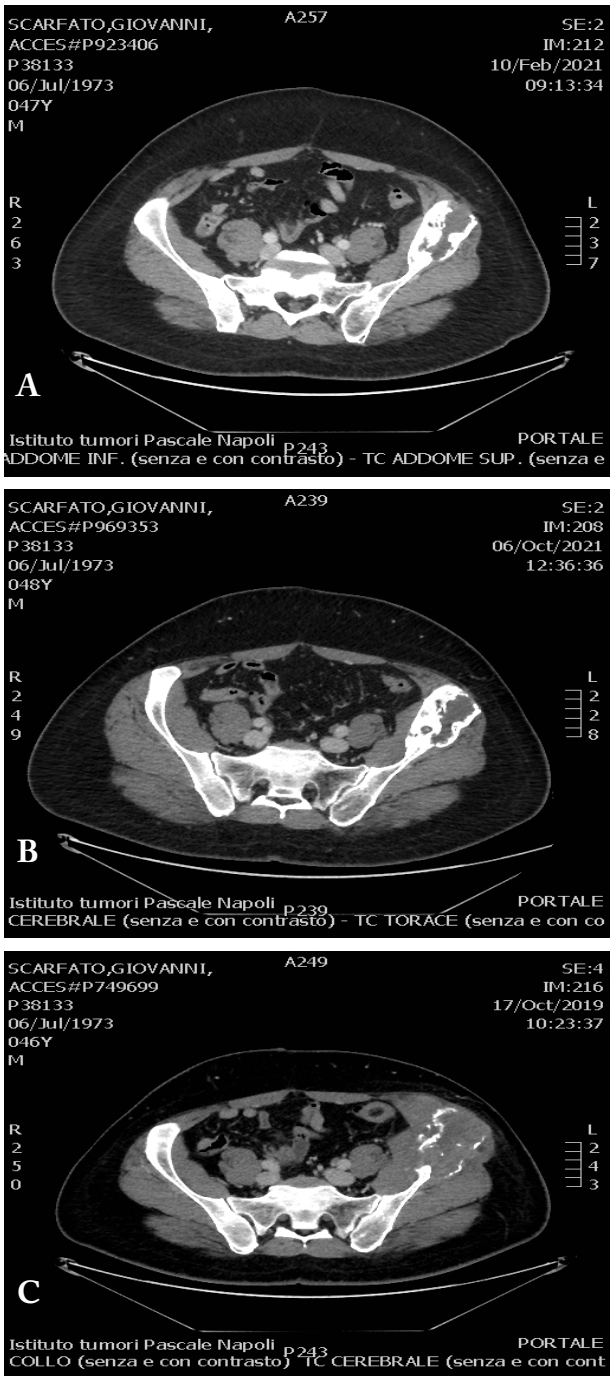

Figure 1. Radiological evolution of the left ilium lesion during the nivolumab–ipilimumab therapy. A: baseline; B: 16 months after the treatment initiation; C: two years after the treatment initiation.

timeframe, before local progression and the detection of a rib metastasis. In a recent retrospective analysis collecting 80 patients suffering from RCC, starting nivolumab–ipilimumab in presence of bone metastases [10], the two-years survival PFS rate was < 25% with a median OS of 25.6 months, confirming the negative prognostic role of skeletal localizations in patients receiving nivolumab [11]. Taking into consideration the elements that characterize the clinical case we described here, the absence of metastases other than the bone lesions was independently associated with a longer PFS, while the rib involvement was a negative prognostic factor. In addition, previous radiotherapy to bone metastases has been independently associated with a longer OS [9]. In our case, radiotherapy was administered for palliative/antalgic reasons, but we cannot exclude that it boosted the radiotherapy efficacy as well [12]. With regard to the COVID-19 diagnosis, no evidence is thus far available regarding a putative increase of severity and mortality in patients suffering from RCC due to SARS-Cov-2 infection, even during ICI treatment [13]. In addition, the patient developed COVID-19 when it was out from the "active" phase of the disease, as a partial response had already been achieved, the disease was under control and the clinical conditions were good.

In conclusion, we presented the case of a patient with an aggressive RCC recurrence at the bone level, who achieved a prolonged benefit (still persistent two years after treatment initiation) with the first-line nivolumab–ipilimumab combination.

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Correspondence:
Received: ?
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Corresponding Author
Dr. Marilena Di Napoli, MD
Department of Urogynecology, National Cancer Institute Pascale Foundation (Scientific Institute for Research and Healthcare)
Via Mariano Semmola, 80131, Naples, Italy
Email address: m.dinapoli@istitutotumori.na.it