Annals of Clinical and Medical Case Reports

Long-Term Response after Early Discontinuation Due to Immunotherapy Toxicity In Metastatic Renal Cancer: A Clinical Case and Literature Review

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1. Abstract

Immunotherapy has a cardinal role in renal cancer, both in adjuvant setting and metastatic disease (first or subsequent lines). Severe immune-related adverse events (irAEs) occur in 10-27% of patients treated with immunotherapy [1,2], but the discontinuation of the treatment due to toxicity doesn't necessarily correlate with poor outcome. We present the case of a woman affected by metastatic clear cell renal cell carcinoma who presented a long-term response to second line treatment with Nivolumab after early interruption due to immuno-toxicity (hepatotoxicity, skin rash, hypothyroidism).

2. Background

Immune-checkpoint inhibitors play a pivotal role in the treatment of renal cancer. In Europe pembrolizumab (antibody targeting the programmed death receptor-1 – PD-1) is approved by European Medical Association (EMA) in adjuvant setting in intermedi- ate-high and high risks of relapse and in M1 NED tumors, accord- ing to the Keynote-564 trial [3]. Several first line trials highlighted the importance of immunotherapy in this setting for clear cell re- nal cell carcinoma, both alone and in combination with anti-angiogenetic TKIs. Nivolumab + ipilimumab (Checkmate-214) [2] is approved by EMA for intermediate and high risk, according to International Metastatic RCC Database Consortium (IMDC) risk model classification; pembrolizumab + axitinib (Keynote-426 tri-al) [4], nivolumab + cabozantinib (Checkmate-9ER trial) [5] and pembrolizumab + lenvatinib (CLEAR trial) [6] are approved by EMA for all the risk class, according to IMDC. In a randomized phase III trial CheckMate 025, nivolumab compared with everoli-mus in pre-treated patients conferred a 5.4-month improvement of median OS, with a more favorable safety profile [1,7]. For the clinical benefit demonstrated with this trial, on April 2016 the EMA approved nivolumab for mRCC patients who had received a prior line of treatment with anti-angiogenic agents. A great number of trials studying immunotherapy in ccRCC are ongoing in this moment, in all the settings.

Regarding the tolerability to immunotherapy, immune-checkpoint inhibitors (ICIs) induce a peculiar spectrum of toxicities, different from the one determined by conventional chemotherapy, caused by an enhanced activity of the immune system and by systemic inflammation: the so-called "immune-related adverse events" (irAEs) [8]. They can involve different tissues with a wide variety of manifestations, generally mild, even if moderate-severe ones can occur. IrAEs could be dermatological (rash, pruritus), gastro-intestinal (colitis with diarrhea, hepatitis, pancreatitis), pulmonary (pneumonitis), endocrine (thyroiditis, diabetes mellitus, hypo-physitis), renal (nephritis) and systemic (fever and fatigue) [9]. In mRCC G3-G4 irAEs develop in 1.7–19% of patients treated with anti-PD-11 and 1.3–10.4% of patients treated with anti-PD-1 + anti CTLA-42. G5 (fatal) irAEs have been reported in almost 0.36% of patients treated with anti PD-1/PD-L1, 1.08% in those treated with anti-CTLA-4 and 1.23% of patients treated with the combination of both [10].

3. Clinical Case

The patient is a 76 years caucasic non-smoker female with hypothyroidism, diabetes mellitus insuline-dependent, vitiligo and hypertension as comorbidities, well controlled with specific therapy. In March 2020 a thorax-abdomen CT scan, performed during follow up for previous pT1 N0 rectal cancer, revealed a left renal lesion (3.6 x 2.9 cm), a para-aortic lymphadenopathy and a liver lesion (1.7 cm). The biopsy of the renal mass suggested diagnosis of renal cell carcinoma, clear cell variant (ccRCC), and the biopsy of the liver lesion confirmed the diagnosis. No relevant laboratory findings emerged, so the tumor was classified as intermediate risk metastatic renal cancer, according to International Metastatic RCC Database Consortium (IMDC) score. Therefore, we decided to start a first line treatment with Cabozantinib (according to the results of CABOSUN study [11]; after 8 months from the start, the CT scan evidenced a progression in both hepatic and renal lesions and the appearance of new retroperitoneal lymphoadenopathies.

Thus, in February 2021, we started a second line treatment with Nivolumab, according to guidelines. After one cycle, a G2 skin macular rash in décolleté region and arms appeared and the laboratory showed G1 asymptomatic hypothyroidism, exacerbation of diabetes mellitus (glycemia 250 mg/dL), worsening of vitiligo and G3 hepatotoxicity (GOT/GPT 281/527 G3 DR, ALP 210 G1 DR). According to ESMO guidelines, we confirmed no relevant risk factors or causes for liver enzymes elevation in patient's anamnesis, we carried out HBV, HCV testing and performed a liver US, with negative results. Therefore, a high corticosteroid treatment was started (1 mg/kg) and Nivolumab was discontinued. The monitoring of liver enzymes showed a normalization in almost a month and the patient continued with clinical and radiological follow-up. Now, after 2 years and 7 months without a treatment, the patient is still in partial response, highlighting that the disease is still responding to the only cicle of immunotherapy (Figure 1).
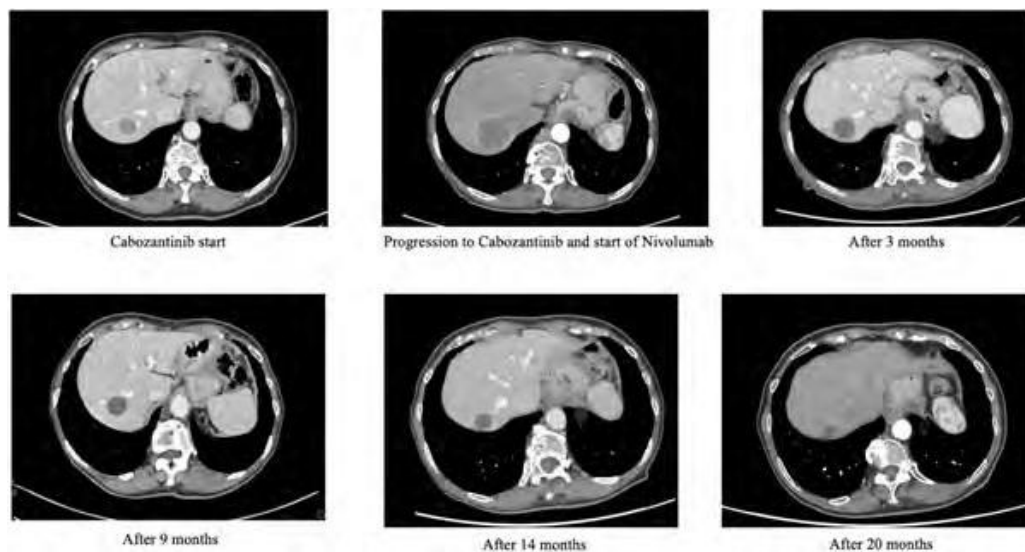
Figure 1: Literature review on the association between irAEs onset and response to IO

3.1. Rational

The rational of the possible correlation between the occurrence of irAEs and response to IO is not clear. The unbalancing of the immune system induced by ICI could be developed by cross-reactivity between tumor neoantigens and normal tissue antigens [12]; concerning CTLA-4 antibodies, ipilimumab possibly induce a non-specific increase in endogenous T-cell response mediated by dendritic cells or paracrine cytokine stimulation [13]; furthermore, considering anti-PD-1/PD-L1 inhibitors, they can modulate B cells' activity with the production of auto-antibodies potential causes of irAEs [14]. Even if various hypotheses have been formulated, the reason why there is a potential association between irAEs during PD-1/PD-L1 and/or CTLA-4 treatment and response has to be fully understood yet. Another important question still not completely solved is understanding which biomarkers are involved in occurrence of irAEs (and thus potentially to patient's outcome during immunotherapy). Some studies described that in

clinical practice, pre-existing organ failure is supposed to be associated to higher risk to develop irAEs as well as pre-exiting auto-immune disease (AID) [15–19]. Talking about molecular biomarkers, Tahrini et al. described that the baseline circulating Interleukin (IL)-17 was related to G3-G4 colitis [20]. Other studies focused on the gut microbiome: significant differences in microbial diversity and composition have been noted between responding and non-responding melanoma patients treated with anti-PD-1 therapy, suggesting that different species may be enriched in responding versus non-responding patients [21,22].

3.2. Multipatology and Rcc Studies

Among the last 20 years, more than 50 studies about the correlation between irAEs and outcome (in terms of ORR, PFS and OS) were conducted [23]. Most of the studies regarded melanoma and lung cancers, while only a few were about renal cell carcinomas. Even if earlier studies in melanoma patients suggested no association between irAE onset and anti-cytotoxic T-lymphocyte-asso-

ciated protein 4 (CTLA-4) antibody efficacy [24,25], subsequent bigger and multi-pathology studies demonstrated a relationship irAEs / response to IO.

A secondary analysis of CA209-003 trial, studying the 5-year outcomes in patients with renal cell cancers, lung cancers and melanomas, resulted in an overall survival significantly longer among patients with treatment-related AEs of any grade (median, 19.8 months; 95% CI, 13.8-26.9 months) or grade 3 or more (median, 20.3 months; 95% CI, 12.5-44.9 months) compared with those without treatment-related AEs (median, 5.8 months; 95% CI, 4.6-7.8 months) (P < .001 for both comparisons based on hazard ratios) [26]. Another retrospective analysis of 157 patients with different histologies demonstrated a PFS benefit, regardless the use of systemic corticosteroid [27].

A prospective study on 73 NSCLC patients treated with immunotherapy displayed that autoimmune skin toxic effects were more frequent in patients with complete remission or partial remission (68.2% [95% CI, 47.3%-83.6%]) than those with progressive or stable disease (19.6% [95% CI, 11.0%-32.5%]) [28]. Rogado et al, studied patients treated with single-agent nivolumab or pembrolizumab for advanced cancer; among 106 patients, irAEs were observed in 40 patients; 33 of the 40 patients with irAEs had objective response (82.5%) in contrast with 11 of the 66 cases without irAEs (16.6%) (OR 23.5, p < 0.000001). PFS in patients with irAEs was 10 months and 3 months in those without irAEs (HR 2.2, p < 0.016). OS was 32 months and 22 months in patients with irAEs and in those without irAEs, respectively, without statistically significant differences [29]. Other studies with melanoma or lung cancers highlighted more or less the same results [30–35].

Regarding RCC, a few studies were conducting; according to Verzoni et al [36], patients treated with Nivolumab in subsequent setting who developed irAEs (early or late onset) versus those ones who didn't develop irAEs had a more significant survival benefit (median OS not reached versus 16.8 months, p = 0.002). The occurrence of irAEs displayed a strong association with OS in univariable (HR 0.48, p = 0. 003) and multivariable (HR 0.57, p = 0.02) analysis. A retrospective study tested body mass index (BMI), irAEs and gene expressions as potential biomarkers associated with resistance and outcomes in RCC [37]. In 90 patients treated with either pembrolizumab, nivolumab or atezolizumab, 26.7% developed irAE median PFS was 20.5 months vs 10.1 months in irAE+ versus irAE- patients (HR 0.42, 95% CI 0.17–0.99, p = 0.04); however, no difference in median OS was noted (28.73 versus. 30.67 months in irAE+ versus irAE− patients, respectively (HR 0.80, 95% CI 0.20–3.19, p = 0.75). Elias et al. studied 90 metastatic RCC patients treated with various ICIs [56]; median OS was 35.9 months versus 26.5 months in irAE + versus irAE- patients (HR 0.376 – 95% CI 0.179–0.792; p = 0.010) [38].

3.3. Implication of Onset Time of Iraes

The implications of timing of irAE onset and ICI efficacy have been much less studied. Previously referenced studies in NSCLC and gastrointestinal cancer patients have not demonstrated a relationship between earlier irAE onset and increased ICI response. A study in melanoma patients also did not demonstrate this relationship [39]. On the other hand, another previous study conducted by Rogado et al29 on G3-4 irAEs seem to be related to efficacy of IO even when treatment is early interrupted due to toxicities. Recently, Stellato et al, demonstrated the efficacy of IO even after early interruption due to irAEs [40]. In this study, the author retrospectively collected data from 204 mRCC patients treated with ICIs in 6 Italian referral centers adhering to the Meet-Uro group, comparing those who had early severe (G3-G4) irAEs (study group, n=18) with those who had not (control group, n=186). Among the study group, 12/18 (66.6%) were free from progression at 6 months since IO interruption, TTF was 1.6 months (95% CI 1.6–2.1), mPFS was 7.4 months (95% CI 3.16–11.6) and mOS was 15.5 months (5.1–25.8). In the control group 111/184 (60.3%) patients were free from progression at 6 months, TTF was 4.6 months (95% CI 3.5–5.6), mPFS was 4.6 months (95% CI 3.5–5.6) and mOS was 19.6 months (95% CI 15.1–24.0).

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