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A comprehensive review of the role of immune checkpoint inhibitors in brain metastasis of renal cell carcinoma origin

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ABSTRACT

The contribution of renal cell carcinoma (RCC) to brain metastases (BM) reaches 7–13%. These patients have limited survival with local control and targeted therapies. Immune checkpoint inhibitors (ICI) revolutionized the treatment landscape of RCC but commonly excluded BM patients from their pivotal trials. The daily clinical practice often imposes the use of ICI in RCC patients with BM in view of the promising survival times and durations of response. Only small prospective trials have included BM patients but rarely reported on the efficacy or safety of ICI in this subgroup. The available data is limited to small retrospective and prospective series that have shown comparable efficacy to that of the pivotal trials. In this review, we will discuss the biological rationale and potential concerns for the use of ICI in BM RCC. Furthermore, we will summarize BM subgroup data from the prospective and retrospective series of ICI in RCC as well as the use of cranial radiation and ICI.

1. Introduction

Metastatic renal cell carcinoma (mRCC) occurs in 25–30% of patients at diagnosis and develops in 40% after surgical treatment in localized stages (Choueiri and Motzer, 2017). Brain metastases (BM) are not a rare finding in mRCC as the 5-year cumulative incidence of BM RCC reaches 9.8% (Schouten et al., 2002). Other retrospective series report similar incidence of BM from RCC reaching 7 to 13% (Ernest Marshall et al., 1990; Seaman et al., 1995; Ljungberg and Rasmuson, 1999; Shuch et al., 2008; Sun et al., 2018). The median overall survival (OS) of untreated patients with RCC BM averages 3 to 4 months (Decker et al., 1984). The indications for local control in BM, including stereotactic radiotherapy (SRT), surgery or whole brain radiation (WBRT), depend on the symptoms, number, size and locations of BM as well as the performance status of the patients (Remon et al., 2012). The addition of systemic treatments with tyrosine kinase inhibitors yielded an objective response rate (ORR) of 12% and median overall survival (OS) of 9.2 of months (Sun et al., 2018; Gore et al., 2011). Still, the trials of RCC strictly excluded patients with BM in 24% whilst 57% enrolled BM with contingencies of local control or absence of symptoms (Le TC, 2017). Recently, immune checkpoint inhibitors (ICI) have revolutionized the treatment armamentarium of mRCC across the different treatment lines with promising efficacy outcomes and tolerable safety profiles (Wallis et al., 2018; El Rassy et al., 2017). These advances changed the standard of care of mRCC as manifested in the recently updated guidelines (Escudier et al., 2016a; Powles et al., 2018a).

The limited survivals of BM RCC patients challenge the role of ICI in these patients as they are often excluded from the pivotal trials (Motzer et al., 2018a; Atkins et al., 2017; Motzer et al., 2018b, a; Motzer et al., 2015b). The backdrop for this exclusion relies on the increased size of ICI which limits their ability to cross the blood-tumor-barrier, the use of steroids to resolve symptomatic edema of BM which may alter the activity of the immune system and the risk of pseudoprogression and hyperprogression (Parvez et al., 2014; Kobari et al., 2017; Soria et al., 2018). Moreover, BM patients often need radiation therapy for local control and safety data of the combination cranial radiation plus ICI remains sparse. This combination seems to provide an opportunity to block the brakes of the immune system and to boost the abscopal response rates (Ngwa et al., 2018). As limited studies have assessed the role of ICI in RCC with BM which challenges the generalizability of the promising data of ICI in mRCC. Therefore, we undertook this comprehensive review of the literature in order to better understand the biological rationale, benefits and risks of ICI in the management of mRCC with BM.

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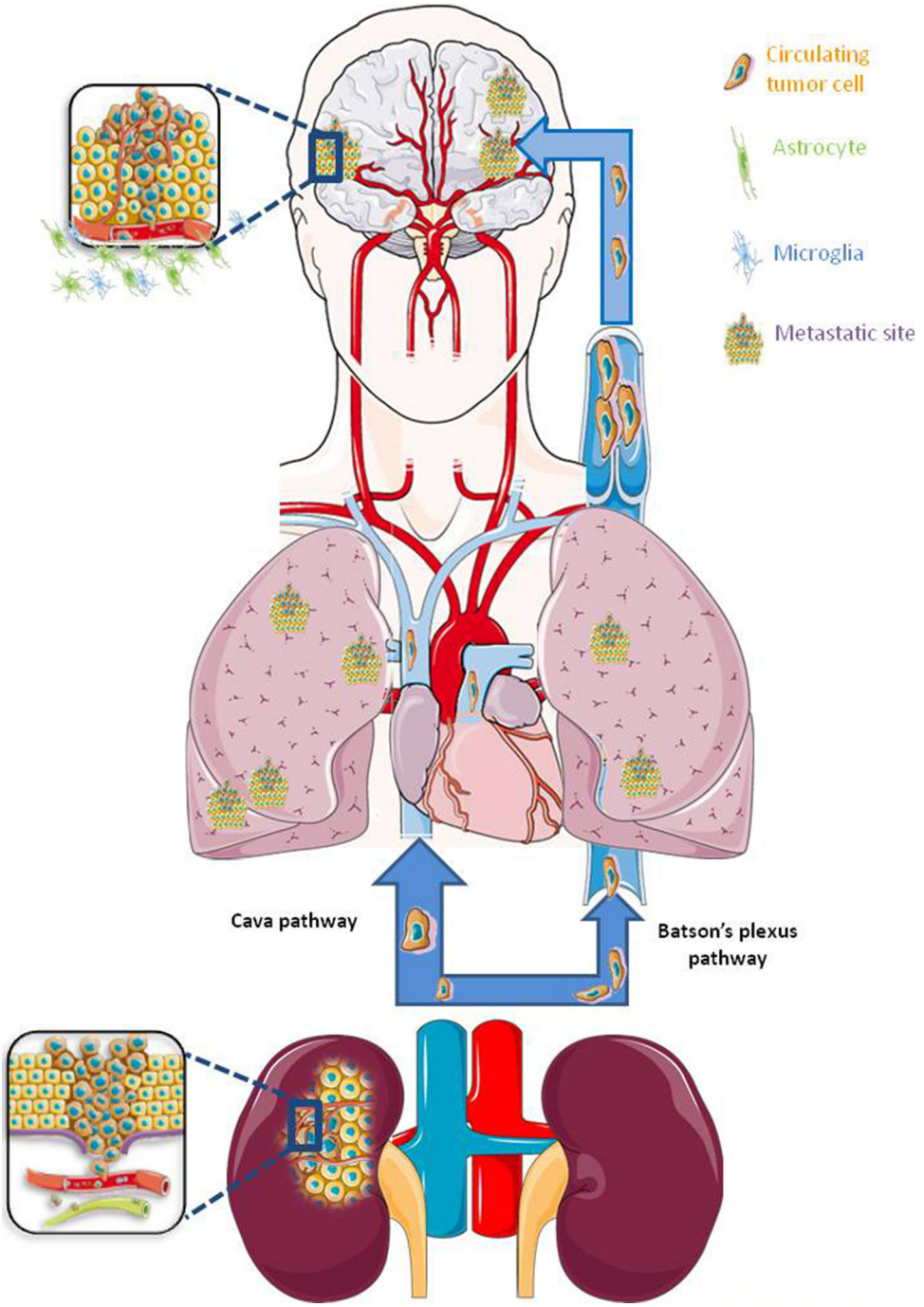

Fig. 1. The pathways and successive steps in the development of brain metastasis in renal cell carcinoma.

2. Brain metastasis development and interaction with the blood-brain-barrier

The increased prevalence of BM from RCC origin may be explained by the presence of additional dissemination pathways for RCC that are not available for other tumors (Schouten et al., 2002; Wyler et al., 2014). As the vasculature of RCC is identical to the kidney, all caval blood from the renal veins flows to the lungs thus BM RCC is thought to metastasize according to the cava-type in 75% of the cases (75%) (Wyler et al., 2014). Alternative pathways may also exist through the Batson's plexus as 25% of BM RCC may occur in the absence of lung metastasis (Fig. 1) (Wyler et al., 2014; Bubendorf et al., 2000).

Another complementary explanation for the increased percentage of BM RCC is the better survival of RCC in the brain than the other tumors (Schouten et al., 2002; Wyler et al., 2014). The metastatic spread is hypothesized to begin with RCC-derived microvesicles CD105+ which break off from the primary tumor site and disperse through the hematogenous route. These microvesicles carrying a cancer stem cell phenotype and microRNAs which stimulate angiogeneisis are transported by the right heart into the pulmonary capillaries and arterial circulation to attain the cerebral vasculature (Grange et al., 2011). At this level, cancer cells usually arrest at vascular branching where they attach to endothelial cells and initiate transendothelial migration (Preusser et al., 2012). Cancer cell attach to CXCL12 which is highly expressed in brain tissue via the CXCR4 receptor that is commonly induced by the regulator of RCC, the Hypoxia Inducible Factor-1α (Pan et al., 2006). Moreover, cancer-cell-derived CCL2 and CCL7 attract CCR2-positive endothelial to disrupt the blood-brain-barrier by