Adamantinomatous Craniopharyngioma Treatment

Therapeutic modalities for children with Adamantinomatous Craniopharyngioma include maximally-safe surgery, radiation, and cyst-directed therapies, such as interferon and bleomycin. None of these approaches, however, are directed against unique biological characteristics of ACP. Furthermore, after many years of use, each has been shown to be associated with shortcomings regarding clinical efficacy and/or side effects [1) 2) 3) 4) 5)].

Aberrations in the CTNNB1 gene lead to the dysregulation of the Wnt pathway and the accumulation of nuclear β-catenin, which may play a role in tumor invasiveness. While Wnt pathway/β-catenin inhibition may be a promising treatment for ACP, potential off-target effects have limited its use in current intervention strategies. Promising evidence of the therapeutic potential of cystic proinflammatory mediators and immunosuppressants has been translated into clinical therapies, including interleukin 6 and IDO-1 inhibition. The dysregulation of the pathways of mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), epidermal growth factor receptor (EGFR), and programmed cell death protein 1 and its ligand (PD-1/PD-L1) has led to identification of various therapeutic targets that have shown promise as clinical strategies. The Sonic Hedgehog (SHH) pathway is upregulated in ACP and has been implicated in tumorigenesis and tumor growth; however, inhibition of SHH in murine models decreased survival, limiting its therapeutic application. While further preclinical and clinical data are needed, systemically delivered therapies could delay or replace the need for more aggressive definitive treatments. Ongoing preclinical investigations and clinical trials of these prospective pathways promise to advance treatment approaches aimed to increase patients' quality of life [6)]

Two patients with recurrent cystic ACP were offered systemically administered tocilizumab or a combination of tocilizumab and bevacizumab on a compassionate use basis. Both patients' tumors had a significant response, with decreased cyst burden, supporting the assertion that tocilizumab with or without bevacizumab may be an option for patients suffering from cystic ACP. [7)]

Zhang et al. demonstrated that CD47 plays an important role in adamantinomatous craniopharyngioma cells, suggesting that CD47 could be a new potential therapeutic target for adamantinomatous craniopharyngioma treatment, and adding to the body of literature a role for the inhibition of MAPK/ERK in ACP [8)]

The evolving characterization of the biological basis of adamantinomatous craniopharyngioma (ACP) has provided insights critical for novel systemically delivered therapies. While current treatment strategies for ACP are associated with low mortality rates, patients experience severely lowered quality of life due to high recurrence rates and chronic sequelae, presenting a need for novel effective treatment regimens. The identification of various dysregulated pathways that play roles in the

pathogenesis of ACP has prompted the investigation of novel treatment options. Aberrations in the CTNNB1 gene lead to the dysregulation of the Wnt signaling pathway and the accumulation of nuclear beta-catenin, which may play a role in tumor invasiveness. While Wnt pathway/beta-catenin inhibition may be a promising treatment for ACP, potential off-target effects have limited its use in current intervention strategies. Promising evidence of the therapeutic potential of cystic proinflammatory mediators and immunosuppressants has been translated into clinical therapies, including interleukin 6 and IDO-1 inhibition. The dysregulation of the pathways of mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), epidermal growth factor receptor (EGFR), and programmed cell death protein 1 and its ligand (PD-1/PD-L1) has led to identification of various therapeutic targets that have shown promise as clinical strategies. The Sonic Hedgehog (SHH) pathway is upregulated in ACP and has been implicated in tumorigenesis and tumor growth; however, inhibition of SHH in murine models decreased survival, limiting its therapeutic application. While further preclinical and clinical data are needed, systemically delivered therapies could delay or replace the need for more aggressive definitive treatments. Ongoing preclinical investigations and clinical trials of these prospective pathways promise to advance treatment approaches aimed to increase patients' quality of life [9)].

Early disease onset, clinical manifestation, histomorphology, and increased tendency to relapse distinguish the adamantinomatous craniopharyngioma (adaCP) from the more favorable papillary craniopharyngioma variant (papCP). A molecular hallmark of adaCP is the activated Wnt signaling pathway indicated by nuclear beta-catenin accumulation in a subset of tumor cells. A mouse model recently illustrated that these cells are the driving force in tumorigenesis of adaCP. This observation and the peculiar growth pattern points to the existence of a specific tumor stem cell (TSC) population in human CP. Tumor stem cell-like characteristics of beta-catenin accumulating cell clusters in adaCP, which may represent a tumor stem cell niche and might contribute to tumor recurrence. The potential impact of these special cell groups in regard to future CP management, including postoperative follow-up and additional treatment remains to be explored [10)].

Osteogenic factor Bmp2 may play an important role in the calcification of adamantinomatous craniopharyngioma ACP via autocrine or paracrine mechanisms. Given the presence of osteogenic markers (Runx2 and Osterix), craniopharyngioma cells could differentiate into an osteoblast-like lineage, and the process of craniopharyngioma calcification resembles that which occurs in osteogenesis/odontogenesis [11)].

Adamantinomatous and papillary craniopharyngiomas harbor mutations that are mutually exclusive and clonal. These findings have important implications for the diagnosis and treatment of these neoplasms [12)].

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