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Adrenocortical carcinoma: The management of metastatic disease

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Contents

Abstract

Adrenocortical cancer is a rare malignancy. While surgery is the cornerstone of the management of localized disease, metastatic disease is hard to treat. Cytotoxic chemotherapy and mitotane have been utilized with a variable degree of benefit and few long-term responses. A growing understanding of the molecular pathogenesis of this malignancy as well as multidisciplinary and multi-institutional collaborative efforts will result in better defined targets and subsequently, effective novel therapies.

Keywords: Adrenocortical carcinoma; Therapeutics; Targeted therapies; Metastatic disease

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1. Introduction

Adrenocortical carcinoma (ACC) is a rare and aggressive malignancy of the adrenal cortex with an annual US incidence around 1–2 cases per million population [1,2]. Notably, given reliance of incidence data on NCI surveys from the 1970s as well as the challenge in proper histopathologic diagnosis, the true incidence may be underestimated.

ACC can occur at any age, but there is a bimodal distribution with a first peak at childhood (1–6 years old) and the second peak in the fourth to fifth decade of life [3]. The Surveillance Epidemiology End Results (SEER) data reports an incidence of 0.3 per million in children younger than 15 years. Notably, there is up to 18-fold higher incidence of cases in children in southern Brazil due to environmental and genetic risk factors which have been identified [4]. In this population, germline mutations of the *TP53* tumor suppressor gene (R337H) have been detected in 34% of the patients [5]. In addition to the above demographics, women have a higher incidence compared to men of about 2:1 with studies showing proliferative effects of estrogen on ACC cells, although not establishing this as a clear cause for the higher female incidence [6,7].

Sporadic ACC is a heterogeneous neoplasm with a poorly understood molecular pathogenesis [8]. The relationship between ACC tumorigenesis and familial hereditary syndromes has provided some insights into the molecular biology of this disease (Table 1) [9]. Chromosome imbalances (losses and gains) in specific loci of DNA have been reported with impact on several genes such as *TP53*, insulin-like growth factor type II (*IGF-2*), steroidogenic factor 1(*SF1*) and β-catenin. Given their roles, these genes have been identified as potential candidates for targeted therapies [10–12].

Overall, ACC carries a poor prognosis with the most important prognostic factors being the tumor stage at time of diagnosis. Unfortunately, with the absence of specific cancer-related early symptoms about 70% of patients are diagnosed with stage III or IV disease. In a European series of patients, the 5-year survival rates were 60% for stage I, 58% for stage II, 24% for stage III, and 0% for stage IV. Importantly, the median survival for metastatic disease (stage IV) at the time of diagnosis is less than a year [13].

ACC management often requires a multidisciplinary approach, frequently involving a medical oncologist, an endocrine surgeon, an endocrinologist and several other disciplines. Surgical resection remains the cornerstone of the treatment and represents the only curative option for patients with early stage ACC. However, around 80% of these patients will present local or distant recurrence after a complete resection [14]. With regard to recurrent or advanced disease, ACC is modestly responsive to standard cytotoxic chemotherapies, although various combinations have shown clear palliative benefit. Radiation and ablative techniques have been utilized with variable benefit depending on the clinical scenario.

The above realities highlight the fact that effective systemic treatments for advanced disease are lacking. The pipeline for novel drug development and testing in clinical trials has been limited. The goal of this manuscript is to review the advances in the therapy of advanced ACC. With the recent evolution of new technologies producing genetic data and the molecular characterization of multiple solid tumors described by The Cancer Genome Atlas, we will also focus on the potential of targeted signaling pathways and personalized therapies.

2. Evidence acquisition

A systematic review of the MEDLINE databases was performed on September 2013. The search was conducted using the keywords “general surgery”, “therapeutics”, “mitotane”, “radiotherapy”, “biological markers”, “oncogenes”, “tumor suppressor genes”, “drug therapy” and “adrenocortical carcinoma”. In total, 266 abstracts were identified. Articles about advanced disease were manually selected. Full text of potentially relevant studies (97 articles) were carefully examined by the authors and considered for analysis. Review articles were also analyzed. We searched abstracts and

Table 1
Hereditary ACC-related hereditary syndromes.

Hereditary syndrome	Chromosome alterations	Gene	Comments
Li–Fraumeni syndrome [10]	17p13	*TP53* *hCHK2*	Mutations in TP53 are present in about 25% of sporadic ACC
Beckwith–Wiedemann syndrome [10]	11p15	*IGF-2* *CDKN1C* *H19*	Macroglossia, macrosomia, Wilms' tumor, ACC
Multiple Endocrine Neoplasia I (MEN I) [10]	11q13	*MEN1*	Adrenal adenomas did not present alterations in this locus
Carney syndrome [10]	17q22-24	*PRKAR1A*	53% of sporadic ACC
Lynch syndrome (LS) [9]	2p16 2q31 3p21 2p16	*MSH2* *PMS1* *MLH1* *MSH6*	The prevalence of LS among patients with ACC is 3.2%