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Targeted therapies in metastatic esophageal cancer: Advances over the past decade

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Contents

Abstract

Esophageal cancer is one of the most aggressive malignancies of the upper aerodigestive tract. Despite advances in surgical techniques and multi-modality therapies, the 5-year survival rate remains poor (14%). Over the past decade, efforts have been focused on the field of drug development with the advancement of novel molecularly targeted therapeutic agents. These agents target a variety of cancer relevant pathways such as vascular endothelial growth factor (VEGF) or its receptor, the cyclooxygenase-2 (COX-2), epidermal growth factor receptor (EGFR), and mammalian target of rapamycin (mTOR) pathways. The number of approved targeted agents remains few, with HER-2 inhibitors leading the list for treatment of HER-2 expressing metastatic adenocarcinomas. Novel agents have not yet been widely explored in esophageal cancer. In this review, we will provide a concise and systematic overview of the development of novel targeted therapies currently under investigation for the treatment of metastatic esophageal disease.

Keywords: Targeted therapies; Metastatic esophageal cancer

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1. Introduction

Esophageal cancer (EC) is a highly aggressive tumor. It is the sixth leading cause of cancer-related death worldwide [1]. Globally, there were 482,300 new esophageal cancer cases and 406,800 deaths in 2008 [2]. In the United States, EC is responsible for more than 4% of annual cancer-related deaths and an estimated 17,460 cases of esophageal cancer were diagnosed in 2012, with 15,070 deaths per year expected from the disease [1,3,4]. There are two histological types of EC with distinct clinico-pathologic characteristics: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). ESCC is associated with risk factors that contribute to chronic irritation and inflammation, such as heavy alcohol intake, especially in combination with smoking [5,6]. EAC is increased in the setting of Barrett's esophagus (BE), a premalignant lesion characterized by replacement of the normal esophageal squamous epithelium with a specialized intestinal metaplasia [5]. Recent epidemiological studies have shown that the incidence of EAC in the United States has been increasing over the last three decades; in contrast, the incidence of ESCC has decreased [7]. The increase in EAC incidence is noted mostly in Caucasian men, and has ranged from 4% to 10% per year since 1976, thus exceeding that of other cancer types [8]. Despite advances in surgical techniques and chemotherapy treatments, prognosis and median overall survival rate in patients with metastatic EAC remains poor and does not exceed 8–10 months [9]. Several underlying reasons are responsible for this disappointingly poor survival including: ineffective screening tools, late diagnosis in most cases, and high risk of recurrence after definitive therapy, which is mainly attributed to occult micro-metastasis that usually present at the time of diagnosis [10]. Over the past decade, continued research has focused on understanding the molecular and biological alterations that lead to EC. This has resulted in the development of novel molecularly targeted agents currently under investigation for treating EC. In this review article, we review the currently available treatment options for EC, with a focus on the various targeted agents currently under investigation.

2. Current standard modalities of therapy in metastatic disease

At the time of diagnosis, more than 50% of patients with EC will have an incurable metastatic disease [5]. Multiple factors will determine whether patients will be candidates for systemic therapy, such as the extent of disease, comorbidities, and overall general health of the patient. The goals of treatment in metastatic disease are to improve symptoms through the control of tumor burden and to prolong survival. The potential benefits of receiving cancer treatment must be carefully weighed against the potential risks. Though there are many approaches to the treatment of metastatic disease, the overall survival time remains restricted [1]. In addition, there are other therapies which may be used to improve the quality of life and control symptoms in patients with metastatic disease, such as endoscopic-placed stents and intraluminal brachytherapy. Here, we review different therapeutic modalities for metastatic EC and their impact on clinical outcome.

2.1. The role of chemotherapy

In recurrent metastatic EC, palliative chemotherapy is an option to control cancer-related symptoms and possibly prolong survival. Chemotherapy can be given as single or combined agents (platinum-based therapy is often used). Single agents carry a low response rate ranging from 15% to 35% [15]. One randomized trial comparing single agent chemotherapy using bleomycin with best supportive care showed a cumulative response rate of 15% in patients with esophageal squamous cell carcinoma, but did not demonstrate any survival advantage [15]. Other trials assessed cisplatin both as a single and combined chemotherapy agent for patients with metastatic disease; the reported response rates ranged between 6 and 21% [16–18]. Though there was a promising response rate in some of these studies, this did not translate into a meaningful improvement in survival for these patients (less than 28 weeks) [19]. Taxane (such as paclitaxel) as a single agent carried a relatively higher response rate of 34% in patients with adenocarcinoma and 28% in those with squamous cell carcinoma, resulting in an overall survival rate of 13.2 months [20]. Data from previous trials using single agent chemotherapies support the observation that sensitivity to chemotherapy is greater in newly diagnosed untreated patients [21].

Various combination chemotherapy regimens have been used in the treatment of advanced metastatic disease. Most of the drugs explored for use as monotherapies have been studied in combination chemotherapy regimens. Cisplatin-based combinations such as CF (cisplatin and 5-fluorouracil) have been widely used and are considered fairly active regimens for advanced and metastatic disease [21]. Triple combination regimens have been studied including: DCF regimen (docetaxel, cisplatin and 5-FU) and the combination of methotrexate, cisplatin and 5-FU [22,23]. A multicenter phase II clinical trial sponsored by Memorial Sloan-Kettering Cancer Center is investigating the effect of modified docetaxel, cisplatin, and fluorouracil (mDCF) in unresectable or metastatic gastric and gastroesophageal adenocarcinoma. In general, studies comparing combination to mono-chemotherapy in patients with metastatic disease have reported a significantly higher response rate, but no significant improvement in the overall survival rate [12,24].

The addition of palliative radiotherapy has been studied in various clinical trials for patients with metastatic EC. In one study, adding 40 Gy of radiation to the primary disease site to 5-fluorouracil and cisplatin revealed improved dysphagia in 75% of patients with a response rate of 55%, and 1-year-survival rate of 45% [25]. Palliative CRT effectively improved dysphagia and 5-year survival rate (15% with median

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