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Complete and Sustained Objective Response per RECIST to Irvalec (PM02734) in Undifferentiated Large Cell Esophageal Adenocarcinoma: A Case Report and a Review of the Literature

Ramón Salazar^a Carmen Cuadra^a Marta Gil-Martín^a
Andrea Vandermeeren^b Vicente Alfaro^b
Cinthya Coronado^b

^aInstituto Catalán de Oncología-IDIBELL, Barcelona, and ^bPharmaMar, Colmenar Viejo, Spain

Key Words

Esophageal cancer · Large cell carcinoma · Irvalec · Chemotherapy

Abstract

Undifferentiated large cell carcinoma is a rare entity in esophageal cancer and very few data are available in the literature on this uncommon histological subtype. We report a case of a 58-year-old Caucasian male previously treated with cisplatin/5-fluorouracil, docetaxel and carboplatin/plitidepsin who received treatment with a novel antitumor agent, Irvalec (PM02734), as fourth line. The patient received treatment from July 2006 to July 2009, a total of 49 cycles, at a dose of 2.4 mg/m² as a 24-hour infusion every 3 weeks. He did not present severe complications or unplanned or cumulative toxicities. Complete and durable response according to RECIST was reported. He was alive at the last follow-up on March 2012.

Introduction

Palliative chemotherapy is the main treatment option for patients with metastatic esophageal cancer and good Eastern Cooperative Oncology Group performance status (ECOG PS) [1]. During the last decade, several chemotherapeutic agents [e.g., cisplatin, 5-fluorouracil (5-FU), mitomycin C, irinotecan, vinorelbine, nedaplatin, paclitaxel, or docetaxel] have been evaluated, alone or in combination, in patients with advanced esophageal cancer. However, responses usually have a short duration, with a disappointing median survival of 6–10 months, and with adverse effects often substantial, especially with cisplatin-based regimens. No standard second-line chemotherapy is available yet.

Irvallec (PM02734) is a synthetic cyclic depsipeptide related to kahalalide F, an antitumor compound with marine origin. Irvallec was selected for clinical development as antineoplastic agent based on its *in vitro* activity against human solid tumor cell lines and its *in vivo* activity in hollow fibers (HF) and xenografted human tumors, as well as an acceptable nonclinical toxicology profile [2].

Case Report

A 58-year-old Caucasian male was diagnosed with esophageal adenocarcinoma on July 2004. TNM classification was TXN1M0 and tumor histology showed an undifferentiated large cell carcinoma, HER-2 negative, and with focal positivity for E-GFR and vimentin in <5% of tumoral component, and intensely positive to E-cadherin in 40% of tumoral component. He underwent palliative temporal gastrectomy and began curative treatment with concurrent chemoradiotherapy. He received 7 cycles of cisplatin plus 5-FU between August 2004 and January 2005, and radiotherapy, with complete response. On July 2005, recurrent disease was diagnosed, with adrenal metastasis and paratracheal lymph node. At this time, he received chemotherapy in the advanced setting, consisting of 3 cycles of cisplatin plus 5-FU between September 2005 and November 2005, with progressive disease as best response. So, afterwards he received a second line of chemotherapy with docetaxel between December 2005 and February 2006, with a new disease progression found on February 2006. Then, the patient was enrolled in a phase I clinical trial and was treated with one cycle of carboplatin and plitidepsin between April and May 2006 as third line. The best objective response was stable disease. He discontinued the treatment due to grade 3/4 thrombocytopenia, grade 4 neutropenia and grade 3 transaminases elevation.

On June 2006, the patient was enrolled into another phase I clinical trial and the treatment consisted of Irvallec 2.4 mg/m² as a 24-hour infusion every 3 weeks. The patient had an ECOG PS score of 1 and normal electrocardiogram (ECG). Signs and symptoms comprised mild (grade 1) dysphagia, myalgia and paresthesia. A spiral computed tomography (CT) scan done on June 2006 showed 3 lymph node metastases, 2 of which (located at precaval and interaortocaval nodes) were considered target lesions for tumor assessment according to the Response Evaluation Criteria in Solid Tumors (RECIST), v.1.0, and the other (located at a pretracheal node) was considered a nontarget lesion. The patient received a total of 49 cycles of Irvallec between July 2006 and July 2009. Dosing was always maintained at the initial planned dose of 2.4 mg/m², although dose delay was necessary several times due to grade 2 neutropenia, grade 1 creatinine increase, grade 3 transaminases elevation, or to treatment-unrelated reasons. With respect to tumor response, the summed longest diameter of target lesions was 50 mm at baseline, remained at 50 mm after cycle 2, and then decreased from 30 mm after cycle 4 to 10 mm after cycle 12, disappearing completely from cycle 16 to the end of treatment (the last assessment was done after cycle 49) (fig. 1, fig. 2). In addition, the nontarget lesion at pretracheal node was present until cycle 8, but was not detected from cycle 10 onwards. Therefore, best response according to RECIST was stable disease after cycle 2, partial response after cycles 4 to 14, and complete response after cycle 16 until the end of treatment. Of note, the patient gained weight (up to 15.5% compared to baseline) and his ECOG PS score improved to 0 while on treatment. The patient discontinued Irvallec treatment after cycle 49 given the presence of grade 2 neutropenia which

lasted for more than 2 weeks; this was a criterion considered in the protocol of the phase I clinical trial for treatment termination. Normal neutrophil count was recovered once treatment was discontinued. Time to progression at the end of the phase I trial period (September 2009) was 38.3+ months and overall survival was 38.6+ months. The patient was alive and progression-free at the last follow-up on March 2012.

Discussion

Most primary malignant neoplasms of the esophagus are squamous cell carcinomas (which occur in the thin, flat squamous cells of the upper and middle part of the esophagus), adenocarcinomas (which occur in secreting cells from the lower part of the esophagus), or a combination thereof [3]. Undifferentiated large cell carcinoma is a rare entity in esophageal cancer and very few data are available in the literature on this uncommon histological subtype.

A small number of studies conducted in the United States, Europe and Canada [4–10] have reported an incidence of large cell esophageal carcinoma ranging from 0.25 to 4.5% (table 1). Incidence decreases to 0.25–1.1% in those studies with the largest populations [4, 5, 10]. However, none of these studies informed about response to treatment of this particular histology subtype and, therefore, the evolution and prognostic of these patients remains uncertain. Indeed, large cell esophageal carcinoma is a very rare tumor, and it is unknown whether it requires to be treated as the typical esophageal cancer, according to TNM, or should be managed in a different way (i.e., like small cell carcinoma of esophagus) [11].

This entity has been more recognized in studies conducted in Japan, where some published reports described cases of undifferentiated ‘non-small cell’ carcinoma of the esophagus [12–15]. The incidence reported in Japan (1%) [14] agreed with that aforementioned in United States or Europe [4, 5, 10], but more information on disease and treatment was provided. Some of these cases described metastatic lesions in lower paraesophageal lymph nodes [13], or in gastric body lymph nodes and liver [14]. Indeed, some authors described undifferentiated non-small cell esophageal carcinoma as highly malignant due to rapid tumor progression and distant metastasis [14]. Reinforcing this, other authors concluded that this type of undifferentiated carcinoma is difficult-to-treat, with a poor outcome, and that further studies on additional cases are required to clarify the clinical and pathological significance of this rare tumor in the esophagus [13, 14].

This is the first case in which treatment of one Caucasian patient with this singular histological subtype is described in detail, and the only one in which complete sustained response to chemotherapy alone has been reported. Previous case reports in Japan on patients with undifferentiated carcinomas treated with 5-FU plus cisplatin or 5-FU plus nedaplatin have shown only partial responses ranging from 2 to 61 months [14]. Our patient received Irvalec, a novel investigational agent, administered as fourth chemotherapy line. Tolerability to treatment is a relevant factor when considering palliative options. In the present case, the patient was able to receive a total of 49 cycles during 3 years without severe complications or unplanned toxicities. Of note, no cumulative toxicities were reported in this long time period. Survival in previous cases reported in Japan varied from 10 months to 4 years; many of them were reported from time of palliative surgery [13, 14]. In the current case, survival from diagnosis was

longer than 7 years, 5 of them after having received chemotherapy with Irvalec. Therefore, this is the longest survival reported to date in this rare tumor type.

Disclosure Statement

Andrea Vandermeeren, Vicente Alfaro and Cinthya Coronado are employees of PharmaMar.

Table 1. Incidence of large cell esophageal carcinoma

Reference	Type of study	Location	Patients with esophageal carcinoma	Patients with large cell esophageal carcinoma	Incidence of large cell esophageal carcinoma, % over total patients
Trivers et al. [4]	Epidemiological survey	United States	65,926	164	0.25
Sgourakis et al. [10]	Retrospective survey (one center)	Germany	437	5*	1.1
Schlansky et al. [5]	Retrospective survey (one center)	United States	131	1*	0.8
Choong et al. [8]	Phase II trial (docetaxel-based chemoradiotherapy)	United States	78	3	3.9
Kok et al. [6]	Exploratory study (human papillomavirus)	The Netherlands	63	3	4.5
Muijs et al. [9]	External beam radiotherapy + intraluminal brachytherapy	The Netherlands	62	1	1.6
Safieddine et al. [7]	Health-related quality of life survey	Canada	52	2	3.9

* Undifferentiated carcinoma (not clearly detailed if large cell).

Fig. 1. Computed tomography scan showing a precarinal lymph node metastasis in a 58-year-old male patient with large cell, undifferentiated esophagus adenocarcinoma before treatment (20 mm) (A) and the complete response obtained after 16 cycles of treatment with Irvalec 2.4 mg/m² as a 24-hour intravenous infusion every 3 weeks (B).

Fig. 2. Computed tomography scan showing an interaortocaval lymph node metastasis in a 58-year-old male patient with large cell, undifferentiated esophagus adenocarcinoma before treatment (30 mm) (A) and the complete response obtained after 16 cycles of treatment with Irvalec 2.4 mg/m² as a 24-hour intravenous infusion every 3 weeks (B).

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