

Squamous-Cell Gallbladder Carcinoma: How to Treat?

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Abstract

Squamous-cell gallbladder carcinoma is a very rare cancer with very few therapeutic data available in the literature. We describe a case of this rare disease with a good response under Gemcitabine and Cisplatin after several previous lines of chemotherapy, in an 80-year-old man. In our case, the disease was resistant to FOLFOX, FOLFIRI and Paclitaxel but an impressive partial response was shown after 9 cycles of Gemcitabine and Cisplatin in fourth-line of chemotherapy. Unfortunately, a progression occurred after 12 cycles (7 months). With the intent of finding a new therapeutic option a molecular analysis was performed using Next-Generation Sequencing and two mutations of *ERBB2* and *PTEN* were found. A standard regimen of chemotherapy for squamous-cell gallbladder cancer does not exist and, because of the rarity of this type of cancer, therapeutic trials will probably never be conducted. The end point of this works is to describe this interesting case and make a review of the literature about treatments used for squamous-cell carcinoma of the gallbladder.

Keywords: Gallbladder; Cancer; Squamous-cell carcinoma; Chemotherapy

Introduction

Adenocarcinoma of the gallbladder is the most common histological subtype representing approximately 90-95% of all cases of gallbladder cancer; in contrast, primary squamous-cell carcinoma or "epidermoid carcinoma" and adenosquamous carcinoma are rarely reported and constitute only 1-12% of gallbladder cancers. The incidence of pure squamous-cell carcinoma drops down to 0 to 3.3% [1].

Squamous-cell carcinoma and adenocarcinoma have similar demographic and biochemical profile, it is predominantly incident among females and between the fourth and sixth decades of life. Squamous-cell carcinoma of the gallbladder is most often diagnosed at an advanced stage and is considered more aggressive and of worse prognosis than adenocarcinoma. This rare case of cancer is known to metastasize to unusual sites such as skin and subcutaneous tissues [2-4]. Some publications reported that squamous-cell carcinoma may be less often associated with nodes metastasis but this point is discussed in the literature [4].

The carcinogenesis and biological behavior of squamous-cell carcinoma have not been clarified and the literature is mostly represented as individual cases reports or small series. In most cases diagnosis is incidental after surgery for cholecystitis [1,5-8].

For gallbladder adenocarcinoma, complete surgery with R0 resection is the cornerstone of therapy and the recommended treatment is surgical resection with cholecystectomy, liver resection block and lymphadenectomy with or without removal of the biliary tract [9,10]. Several authors have proposed an adjuvant treatment including radiation therapy with or without concomitant chemotherapy with 5-fluorouracil and leucovorin [9,11]. Nevertheless, the benefit of radiotherapy or concomitant chemoradiotherapy after surgery remains controversial. For inoperable adenocarcinomas, standard treatment is based on chemotherapy with Gemcitabine plus Cisplatin since the results of the ABC-02 trial [12-14]. None prospective study has been conducted in patients with squamous-cell carcinoma of gallbladder and

data reported in the literature are limited. Only few therapeutic data have been reported from cases report or small series [1,2,7,9,11,15,16].

The aim of this work was to describe a case of patients with a gallbladder squamous-cell cancer with a review of the literature.

Case Report

A 80-year-old man, with antecedents of prostate resection for cancer and abdominal aortic aneurysm, consulted for fever and digestive problems since 6 weeks at the emergency of our center.

Presentation at diagnosis

On abdominal examination a mass in the right hypochondrium was found. Abdominal ultrasonography and computed tomography showed thickened gallbladder with dilatation of bile ducts and gallstone of the lower common bile duct. Laboratory tests showed hypertransaminasemia and cholestasis with normal bilirubinemia and CEA (CarcinoEmbryonic Antigen). The diagnosis of cholecystitis was laid and the patient underwent subcostal cholecystectomy. Histological examination showed a well-differentiated squamous-cell carcinoma with pT3 Nx M0 stage. The surgical hepatic margin was involved by the tumor (R1 resection) and, therefore, the patient underwent secondary segmentectomy (segments IV and V) and dissection of the hepatic pedicle two weeks later. None node was involved among the two nodes examined.

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Follow-up after surgery

The patient started adjuvant chemotherapy with FOLFOX four weeks after second resection. This therapeutic decision was made during a multidisciplinary meeting. In September 2013, after 5 cycles of adjuvant FOLFOX, the patient underwent laparotomy due to an occlusive syndrome with resection of a nodule of carcinomatosis. The CT scan realised four weeks after the surgery confirmed the progression of the disease with presence of metastases in the abdominal wall. A chemotherapy second-line with FOLFIRI was begun without efficacy and a disease progression occurred after 5 cycles. Therefore, the patient began Paclitaxel as chemotherapy third-line with a progression disease after two cycles (two months). In Mars 2014, a fourth-line of chemotherapy with Gemcitabine and Cisplatin was started. A partial response was objectified after 4 cycles, confirmed after 9 cycles with a disappearing of subcutaneous metastases of right hyphochondrium (Figure 1). In Octobre 2014, after a total of 12 cycles of Gemcitabine and Cisplatin, computed tomography showed progressive disease (hepatic and median subcutaneous metastases). Details of chemotherapy regimens used and results are described in Table 1. Because of the relatively good condition of the patient and his wish to receive a new line of treatment, it was decided during multidisciplinary meeting to perform a molecular analysis of the tumor to try to identify a molecular target. In waiting molecular results, metronomic Vinorelbine was begun [17]. Unfortunately, progression of the disease was not stopped and the patient was hospitalized after one month for poor general condition

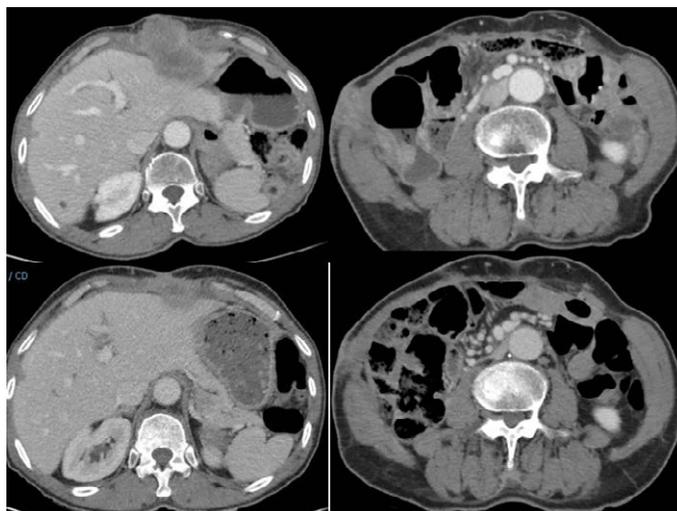
and fever (without documented infection). The patient died 3 weeks later, 22 months after the diagnosis, and without possibilities to begin a new treatment according to found mutations.

Molecular analysis

After DNA extraction, molecular analysis was performed using New Generation Sequencing. DNA was amplified by PCR using the Ion AmpliSeq™ Cancer Colon and Lung Cancer Panel primers pool and the Ion AmpliSeq™ Master Mix v2.0 (Ion Torrent, Life Technologies, Carlsbad, CA) using the recommended manufacturer's protocol. The concentration and size of each multiplexed amplicon library was determined using an Experion™ DNA analysis kit (Bio-Rad Laboratories Inc., Hercules, CA). Sequencing was performed on a Proton Sequencer (Life Technologies). Data analysis, including alignment to the hg19 human reference genome and variant calling, was done using the Proton Suite Software (Life Technologies). Alignments was visually verified and annotated with the ALAMUT software v2.2 (Integrative Biosoftware). Among the 21 genes analyzed (EGFR, AKT, BRAF, CTNNB1, ERBB2, ERBB4, FBXW7, FGFR1, FGFR2, KRAS, MET, NOTCH1, NRAS, PIK3CA, PTEN, SMAD4, STK11, TP53, ALK, DDR2, and MAPK2), two mutations were found: a mutation of ERBB2 (c.2524G>A p.V842I) and of PTEN (c.28_29 insA p.S10fs).

Discussion

Squamous-cell carcinoma is uncommon malignancy of the



Note: Periumbelical (A) and right hyphochondrium (B) metastases before and after (C and D, respectively) 9 cycles of gemcitabine and cisplatin.

Figure 1: CT scans before and after 9 cycles of gemcitabine and cisplatin.

Regimen	Line of chemotherapy	Objective response (RECIST)	Progression free survival (months)
Folfox ¹	Adjuvant (First)	PD (carcinomatosis and subcutaneous metastases)	4
Folfiri ²	Second-line	PD (new hepatic metastases)	2
Paclitaxel ³	Third-line	PD (+ 99 %)	2
Gemcitabine + CDDP ⁴	Fourth-line	PR (- 42 %)	7
Vinorelbine ⁵	Fifth-line	PD	1

Note: 1: leucovorin 400 mg/m² per 2 hours, oxaliplatin 85 mg/m² per 2 hours then 5FU 400 mg/m² bolus then 2400 mg/m² continuous infusion per 46 hours, one cycle every two weeks. 2: leucovorin 400 mg/m² per 2 hours, irinotecan 180 mg/m² per 1 h 30 then 5FU 400 mg/m² bolus then 2400 mg/m² continuous infusion per 46 hours, one cycle every two weeks. 3: paclitaxel 90 mg/m² per hour on days 1, 8 and 15, one cycle every four weeks. 4: cisplatin 25 mg/m² per one hour then gemcitabine 1000 mg/m² per 30 min on days 1 and 8, one cycle every three weeks. 5: oral vinorelbine at a fixed dose of 50 mg three times a week.

PD: Progressive Disease; PR: Partial Response.

Table 1: Description of chemotherapy regimens used and results.

Authors	Patients (n)	Surgery	pTNM stage	Adjuvant treatment	DFS
Bouassida et al. [1]	1	Cholecystectomy	pT4N0M0	Radiotherapy	12 months
Kurniali et al. [14]	1	Right trisectionectomy and bile duct resection	ND	Gemzar	12 months
Soufi et al. [15]	4	Cholecystectomy	ND	Radiotherapy	34 months
Gold et al. [11]	3	Tumor resection	ND	Chemoradiotherapy (5FU)	44.9% at 5 years
Mingoli et al. [16]	2	Tumor resection	ND	Chemoradiotherapy (5FU)	3 months
Rekik et al. [7]	1	Cholecystectomy	pT3N0M0	Chemoradiotherapy (5FU)	12 months
Waisberg et al. [2]	1	Cholecystectomy	ND	Chemoradiotherapy (5FU)	6 months
Bourmèche et al. [9]	1	Cholecystectomy	pT2N1M0	Chemoradiotherapy (5FU)	216 months
Our case	1	Cholecystectomy + segmentectomy	pT3N0M0	Folfox	4 months

Note: ND: Not Described; DFS: Disease Free Survival

Table 2: Adjuvant treatment after curative resection for gallbladder squamous-cell carcinoma.

gallbladder with nonspecific clinical presentation. As consequence of the rarity of this cancer type, none prospective trial has been conducted in patients with gallbladder squamous-cell carcinoma and none prospective study would be probably begin. Thus, therapeutic strategy data published are very limited.

Surgical R0 resection remains the only curative treatment, but only 10-30% of patients can undergo to a curative surgery [18]. As for gallbladder adenocarcinoma, the benefit of an adjuvant treatment has not been proved at yet, and no standard regimen exists. The results of the randomized phase III trial PRODIGE 12 that evaluates the benefit of adjuvant chemotherapy with GEMOX vs. placebo should be presented soon and will maybe help for future therapeutic adjuvant decisions [19].

Fifteen cases of patients who received an adjuvant treatment after curative intent resection for a gallbladder squamous carcinoma have been reported in the literature (Table 2). In most cases, adjuvant radiotherapy with or without concomitant chemotherapy was used [1,6,9,20-22]. The number of reported cases, the heterogeneity of treatment administered and the limited follow-up for most patients do not allow to draw any conclusion. In our case, adjuvant chemotherapy with FOLFOX was decided during multidisciplinary meeting because of the old age of the patient, the safe toxicity profile of this regimen and the squamous-cell histology of the tumor.

After relapse, our patient received three lines of chemotherapy. Because of a progression under FOLFOX and so, a resistant to oxaliplatin, FOLFIRI then paclitaxel were used in second and third lines without any efficacy. Gemcitabine plus Cisplatin regimen was used only in fourth line but was associated with an impressive efficacy at this stage of the disease. For advanced gallbladder adenocarcinoma, this regimen is the gold standard since the results of the ABC-02 trial that reported an increase in overall survival versus Gemcitabine alone (11.7 vs 8.1 months; HR = 0.64; 95% CI 0.52 to 0.80; P<0.001). In this study, only two patients with an adenosquamous carcinoma and one patient with a squamous-cell carcinoma have been included. No detailed data about these three cases are reported in the princeps publication [13]. In the literature, at our knowledge, none clear data about palliative treatment efficacy have been reported. Three cases of patients treated with Gemcitabine plus Cisplatin have been reported in a case series but without data about therapeutic efficacy [23]. In one case, radiotherapy was used in front-line treatment for a locally advanced cancer [24]. A complete response was obtained with a progression-free survival of 13 months and an overall survival of 15 months (no second-line treatment was used) [24].

In the aim to try to find a new therapeutic option and because

of the rarity of this type of cancer, a molecular analysis was decided during multidisciplinary meeting. Two mutations of the ERBB2 and PTEN were found in the tumor of our patient. Unfortunately, the disease progression did not allow us to initiate another chemotherapy line with Trastuzumab. No data has yet been published correlating the molecular profile of squamous-cell carcinoma with the response to therapy but a recent publication has shown that ErbB signalling is one of the most extensively mutated pathways of gallbladder carcinomas [25]. Moreover, the deregulation of the PI3K/AKT pathway seems implicated in gallbladder cell transformation [26].

According with the very low frequency of this type of gallbladder cancer, it does not seem possible that therapeutic trials will be conducted in those patients. Thus, molecular analysis and personalized medicine according to molecular mutations profile could represent an option of choice to try to define new therapeutics options for them.

Conclusion

Gemcitabine and Cisplatin regimen seems to be the best first-line of chemotherapy despite the limited data available in the literature. Molecular analysis is desirable to try to define potential targets for other therapeutic options for these patients.

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