

Intra-Hepatic Cholangiocarcinoma Treated with GEMOX + Cetuximab Protocol

CASE REPORT

Abstract

New studies show a possible benefit of combining Gemcitabine, Oxaliplatin and Cetuximab for the treatment of intrahepatic tumors. However, there is currently no consensus in the literature. Hence, this article contributes to the debate by presenting a case of cholangiocarcinoma (biliary tract cancer), treated with a modified Gemcitabine, Oxaliplatin and Cetuximab protocol, which evolved to a considerable regression of the tumor and a complete radiologic response assessed by PET-CT Scan. The case report is of a female adult, who presented with a cholangiocarcinoma extending to hepatic segments V and VIII which met unresectable criteria. She was submitted to chemotherapy, consisting of a combination of Gemcitabine, Oxaliplatin and Cetuximab for a prolonged period, followed by a maintenance interval of Cetuximab monotherapy. After the 8th cycle, the patient presented better hepatic biomarker levels; after 15 months of treatment, our team achieved optimal partial radiologic response assessed by PET-CT scan as shown; after 15 months of treatment, a MRI scan showed a reduced and resectable tumor. Our case report suggests use of the Gemcitabine + Oxaliplatin (GEMOX) plus Cetuximab protocol as a neoadjuvant setting for patients with unresectable cholangiocarcinoma. Additionally, our case report confirms the GEMOX plus Cetuximab protocol can be modified according to clinical response so patients can obtain maximum therapeutic gain despite minor or adverse reactions.

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Keywords

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Introduction

Intra-hepatic cholangiocarcinoma is a rare tumor of epithelial cells of the biliary tract, with an incidence of 1-2 cases per 100,000 in habitants

in the United States. This tumor has poor prognosis with five years survival rates of only 5-10%. The current treatment of choice is surgery, but in cases of structural impairment of the liver and unresectable tumors, chemotherapy is indicated before surgical treatment [1-5].

The use of Oxaliplatin combined with Gemcitabine (GEMOX) has proven to be highly effective for the treatment of intrahepatic cancer, particularly cholangiocarcinoma. Despite the small increase in the survival rate (four months) of patients who used this combination compared to Gemcitabine alone, it is still relevant to look for new therapeutic alternatives. New studies show a possible benefit in implementing targeted therapy with the use Epidermal Growth Factor Receptor (EGFR) inhibitors, such as Cetuximab, to the GEMOX protocol. This finding has been confirmed by one phase II study [6], which found satisfactory therapeutic responses, while, another study, controversially, found no such benefit [7].

This article is therefore relevant to the debate as it presents the case of a patient with cholangiocarcinoma, who was treated at our institution with a modified GEMOX and Cetuximab protocol, which resulted in a positive outcome.

Case Presentation

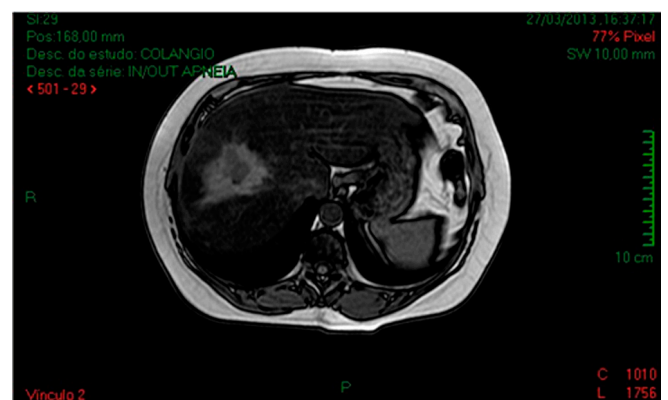
Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

After recommended by her hepatologist, a 56 year-old female patient looked for the oncology clinic with a biopsy result of an intrahepatic tumor. She also had laboratory test results that showed high baseline levels of Gamma Glutamyl Transferrase (Gamma GT) (115 U/L) and alpha-fetalprotein (AFP). Serum levels of aspartate aminotransferase (AST), alanine aminotransaminase (ALT), and lactic dehydrogenase are shown in **figure 2**. The Eastern Cooperative Oncology Group (ECOG) performance status was zero.

Following Magnetic Resonance Imaging (MRI) scans and immunohistochemistry studies for clinical staging and definition of treatment, the patient was diagnosed with intrahepatic cholangiocarcinoma in segments V and VIII. The tumor had a lobulated surface, a baseline diameter of approximately 5 cm (**Figure 1**) and a positive cytokeratin-7. The MRI also showed an increase in the tumor area with some perilesional perfusion abnormalities, unclear margins and a dilatation of the intrahepatic bile ducts. Due to the large size within the liver tree, this tumor was considered unresectable and chemotherapy protocol was performed.

Initially, we opted for the GEMOX (Gemcitabine 1000 mg/m² and Oxaliplatin to 100 mg/m²) plus Cetuximab (250/mg/m² weekly) protocol, which recommends their administration every two weeks for 8 cycles. At her follow-up consult, the patient complained of some expected adverse effects of the chemotherapy like mild asthenia and Grade I rashes, without the need of changing the chemotherapy protocol. After the fifth cycle, the patient had the same mild clinical presentation of adverse effects, as well as a better clinical presentation of her disease. The latter assessment was based on her hepatic function biomarkers, such as Gamma GT (125 U/L), which justified recommen-

Figure 1: Magnetic Resonance Imaging in which liver injury is evident in the segments V and VIII measuring approximately 5 cm.



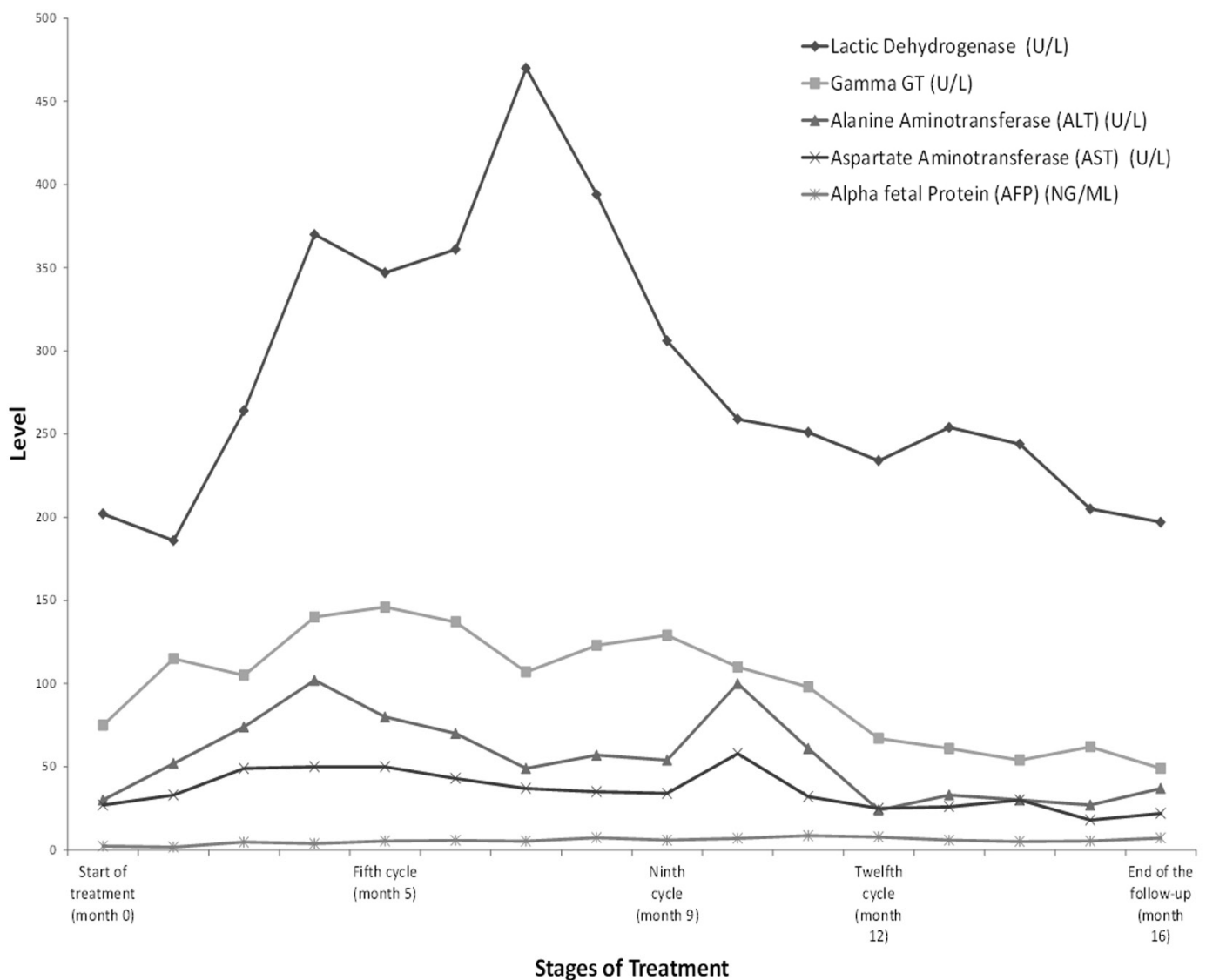
ding her to finish the 12 cycles of the treatment protocol.

She was treated with GEMOX plus Cetuximab until the end of eight cycles and her care was then extended with four more cycles, according to a standard protocol. After completing the 8 cycles of standard approach and 4 administration cycles, we proceeded with Cetuximab (250/mg/m² weekly) maintenance chemotherapy every two weeks. The patient reported only peripheral neuropathy induced by Oxaliplatin, grade II by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE).

After the eighth cycle of treatment, the patient showed reduced hepatic function biomarker levels, with a lower Gamma GT (95 U/L), which continued to fall until the last evaluated cycle (62 U/L). This clinically demonstrates not only the stabilization of the disease, but also its regression either in clinical or laboratorial response. The evolution of patient's biomarkers during treatment can be seen in **figure 2**.

Twelve months after the start of her treatment, positron emission tomography-computed tomography (PET-CT) imaging showed an optimal partial response and optimal clinical response to

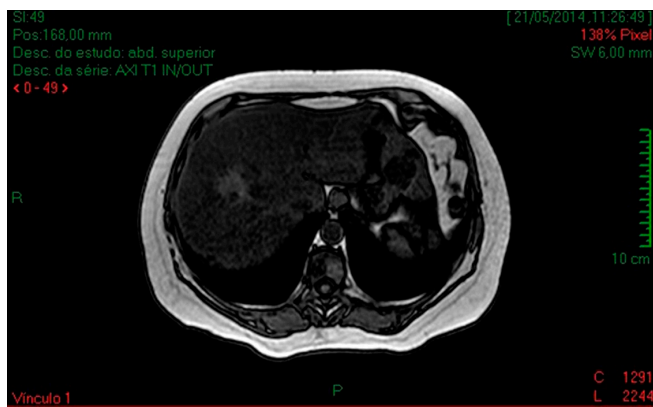
Figure2: Evolution of patient's biomarkers during treatment.



the therapy. After fifteen months of treatment, a MRI also showed a remarkable reduction in tumor size with dimensions of 2.4x1.8 cm at its greatest axis.

Currently, the patient is under surgical evaluation by the hepatology department. She maintains satisfactory radiological responses with a tumor reduced to 2.4x1.8 cm in size (**Figure 3**), and a PET-CT scan showing a complete radiological response.

Figure 3: Magnetic Resonance Imaging in which liver injury is evident in the segments V and VIII measuring approximately 2.4x1.8 cm, after 16 months of treatment.



Discussion

The diagnosis of intrahepatic cholangiocarcinoma is challenging due to the late presentation of symptoms and tumors are often at an unresectable stage at the time of diagnosis. The choice for initial therapeutic approach includes surgery or neo adjuvant chemotherapy [2, 6-8]. The standard primary protocol, GEMOX (Gemcitabine 1000 mg/m² and Oxaliplatin 100 mg/m²), was signed after the ABC-2 Trial, a randomized clinical study that demonstrated an improvement in the overall survival of these patients, with statistically significant results compared to single treatment with Gemcitabine considering adjuvant setting [1].

Even with the improvement in median overall survival of patients treated with GEMOX, patients with advanced biliary tract cancer still have a poor clinical outcome, with an average of less than one year overall survival with treatment. New treatments are continually proposed to increase the overall survival and disease-free survival of these patients [6-8].

Studies with target-specific therapy are being tested and several possible receptors may be related to these types of tumors. Tyrosine kinase receptors for EGFR and for the Mitosis Activator Protein MAPK/ERK kinase (MEK) are found in cholangiocarcinomas and may be relevant for finding alternative therapeutics [1, 6].

A phase II study by Gruenberger et al demonstrated the use of Gemcitabine, Oxaliplatin plus Cetuximab for 12 cycles, in patients with advanced or metastatic intrahepatic cancer. Thirty patients were analyzed with a mean age of 68 years and all were submitted to the same protocol. The study presented satisfactory response rates of 63% in the treated group and three (10%) of these had complete disease eradication [1].

In contrast, a randomized phase II clinical study, BINGO, evaluated 150 patients treated with Gemcitabine and Oxaliplatin. Seventy-six patients were treated with GEMOX plus Cetuximab and the remainder with GEMOX alone. All were given the primary treatment recommended for unresectable or metastatic cholangiocarcinoma. The results showed a median overall survival increase of 1.4 months for those patients treated with the standard GEMOX protocol alone [6].

In our case report, our patient was submitted to the GEMOX plus Cetuximab protocol for 12 months, followed by maintenance with Cetuximab, to which she responded with a considerable clinical regression of the disease for more than 20 months. Subsequently, a PET-CT scan showed complete radiologic response and a MRI showing significant regression of the tumor. In summary, the tumor

that had been unresectable at the beginning of treatment successfully reduced to a size suitable for full surgical resection.

These results show that, despite the recent controversial indications, as suggested by the BINGO study, the GEMOX plus Cetuximab protocol may be effective for some patients, as demonstrated in the study of Gruenberger et al and in this case report. Therefore, we suggest that the GEMOX plus Cetuximab protocol could be used as primary or alternative for patients with a progressing disease submitted to the GEMOX protocol. Additionally, our case report affirms that the GEMOX plus Cetuximab protocol can be modified according to clinical response so patients can obtain a maximum therapeutic gain [6].

Conclusion

Further studies are needed and alternative protocols should be studied in randomized clinical trials to better outline the use of epidermal growth blockers and to develop improved therapeutic strategies in an attempt to increase the survival time of the patient carriers of such tumors with unfavorable prognosis.

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Conflict of Interest Disclosures

The authors declare that there are no conflicts of interest in this case report.

Abbreviations

MRI: Magnetic Resonance Imaging.

PET CT: Positron emission tomography-computed tomography.

AFP: Alpha-Fetalprotein.

AST: Aspartate Aminotransferase.

ALT: Alanine Aminotransaminase.

Gamma GT: Gamma Glutamyl Transferase.

EGFR: Epidermal Growth Factor Receptor.

MEK: Mitosis Activator Protein.

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