Oncology Case Reports Journal

Case Report
Published: 04 Dec, 2020

Combination of Loco-Regional Chemotherapy and Oncolytic Virotherapy to Treat a Metastatic Gastro-Esophageal Tumor

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Abstract

A palliative patient with a refractory end-stage metastatic gastroesophageal tumor did not respond to conventional chemotherapy, lost the ability to swallow, and was considered palliative. She then was treated with Locoregional Chemotherapy (LRC), followed by oncolytic virus immunotherapy with intratumor injection of three Oncolytic Viruses (OV). The extent, size and number of metastases became much reduced, tumor biomarkers improved, and she regained the ability to swallow. Due to her switching to another medical center that did not have ethical approval, she could not continue immunotherapy and expired. These initial encouraging results suggest that a combination of LRC and OV immunotherapy might be an attractive treatment modality for some refractory tumors.

Keywords: Gastric tumor; Oncolytic virotherapy; Immunotherapy; Loco-regional chemotherapy

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Received Date: *30 Oct 2020*
Accepted Date: *27 Nov 2020*
Published Date: *04 Dec 2020*

Citation:
Gesundheit B, Srinivas Raju J, Posen Y, Ellis R, Aigner K, Thaller A. Combination of Loco-Regional Chemotherapy and Oncolytic Virotherapy to Treat a Metastatic Gastro-Esophageal Tumor. Oncol Case Report J. 2020; 3(3): 1029.

Introduction

Metastatic gastric tumors are associated with a median survival of <15 months when treated with cytotoxic chemotherapy [1,2], and <6 months for chemotherapy-refractory tumors treated with immunotherapy [3]. Standard treatments including surgery, chemotherapy and radiation, can prolong survival time, but Quality Of Life (QOL) and long-term responses remain poor, with a high relapse rate.

Cumulative experience with Loco-Regional Chemotherapy (LRC) [4,5], and Oncolytic Virus (OV) [6-8], immunotherapy has shown good therapeutic effects on the primary tumor, metastases and disease status.

Presented are the clinical and radiological responses to LRC combined with intratumorally-injected OV in a palliative patient with a refractory end-stage metastatic gastroesophageal tumor. Although the patient did not survive long after therapy discontinuation, the very good initial therapeutic response showed the clinical potential of the combined treatment.

Case Presentation

A previously healthy 36-year-old woman complained of heartburn persisting for more than 12 months, which increased in intensity during her first pregnancy. At gestational week 24 (01-2019), gastroscopy showed a suspicious finding at the Gastro-Esophageal Junction (GEJ). Biopsy from the distal esophagus and cardia of the stomach documented poorly to moderately differentiated adenocarcinoma that was HER2+ (score =3), CK-7+ and focally CK-20+. MRI work-up (04-2019) showed multiple metastases in the liver, retroperitoneal lymph nodes and vertebra L-1,which aligned with greatly increased levels of tumor markers carcinoembryonic antigen (CEA) of 219 ng/mL (normal <3 ng/mL) and carbohydrate antigen 19-9 (CA19-9) of 108,000 U/mL (normal <37 U/mL). A baseline abdominal MRI showed the primary tumor as an irregular, concentric, short-segment, circumferential wall thickening at the GEJ that blocked the lumen, as confirmed by barium swallow. There was no evidence of adjacent organ infiltration; however, there were nodal metastases to the retroperitoneum with extensive liver deposits (up to 60), a few sub-centimeter lung nodules, and bone metastases. An interim follow-up CT performed 2 weeks later showed an unchanged primary malignancy and metastases, but showed fewer liver lesions. After aborting her pregnancy, the patient

underwent 9 cycles of FOLFOX chemotherapy and trastuzumab (04-2019). The treatment was complicated by episodes of neutropenia and sepsis, which required 4 days in an Intensive Care Unit (ICU). Lower back pain due to metastatic disease was treated with 5 sessions of local radiation. Suspected pulmonary embolisms were treated with prolonged anticoagulation therapy. Shortly after completion of chemotherapy (09-2019), the patient's clinical condition deteriorated; she was unable to swallow, tumor markers were further increased, and PET/CT (10-2019) showed progressive disease at the GEJ with viable tumor tissue (3.7 cm), further dissemination of metastases in the liver and bones (sacrum, vertebra L1, scapula, sternum), and three new pulmonary lesions. The patient required total parenteral nutrition and hospital admission for Intravenous (IV) antibiotics due to fever and neutropenia, and subsequently received palliative radiation at the affected GEJ region. Due to tumor progression, the patient was declared palliative.

After signing informed consent for individual compassionate use of innovative therapies, the patient received the following experimental combination treatment (23 Oct): High-dose LRC (cisplatin, adriamycin, mitomycin c) was administered under angiographic guidance, *via* the right femoral artery to the celiac axis, combined with isolated upper abdominal perfusion (15 min), while the venous return was blocked. Chemotherapy was washed out by chemo-filtration to reduce systemic side effects [9]. The second LRC cycle (20 Nov), which was to be administered 14 days thereafter, was postponed by 14 days due to prolonged neutropenia. Three days after each LRC cycle, a 10% rise in CA19-9 levels was observed, which, after cycle 1 was followed by a 40% drop from the pre-LRC baseline over the 12 subsequent days, and, in cycle 2, was followed by a 60% drop from baseline levels over the 18 subsequent days (Figure 2). Nevertheless, the patient remained unable to swallow, and barium contrast studies showed total GEJ obstruction. Two weeks later (4 Dec), a mixture of the OVs Newcastle disease virus, vaccinia virus and parvovirus was endoscopically injected into the tumor tissue. Within <3 days, the patient was able to drink liquids for the first time in 3 months, as confirmed by radiological passage of barium (Figure 1A). The patient received IV antibiotics to treat a bacterial infection associated with the IV line and was transferred to another medical center. An emergency chest, abdomen and pelvis CT performed (18 Dec) following complaints of acute abdominal pain, showed interval development of long-segment colonic wall thickening with peri-colonic fat stranding and fluid in the pelvis, possibly related to known drug-toxicity. The primary GEJ tumor showed marginal decrease in wall thickening with heterogeneous appearance, possibly related to foci of intramural micro-necrosis, supported by barium pass-through, suggesting functional relief of the mechanical obstruction. The most remarkable immediate changes were the complete resolution of all lung nodules, of retroperitoneal nodes and of most liver lesions. The three residual lesions with slightly increased size, central necrotic umbilication and peripheral rim of uptake, likely represented tumor pseudo-progression as part of an immune-mediated response.

The post-OV-LRC PET-CT performed 8 months after the baseline imaging, showed relatively stable appearance of the concentric GEJ mass, with intense metabolic uptake corresponding with unchanged neoplastic etiology. There was significant interval resolution of liver lesions with only two foci of moderate uptake (Figure 1B). There was a slight increase in the size and number of lung nodules, with some uptake (Figure 1C), which was indeterminate for an immune-mediated response *vs.* progression. The retroperitoneal lymph nodes were decreased in size, without significant uptake (Figure 1D). Low-moderate uptake was observed in multiple bone lesions with accompanying sclerosis (Figure 1E), some of which were occult on the previous imaging modalities. Focal low-moderate uptake in some new mesenteric nodes and the left deep pectoral node, indeterminate for immune-mediated response *vs.* new metastases, was noted.

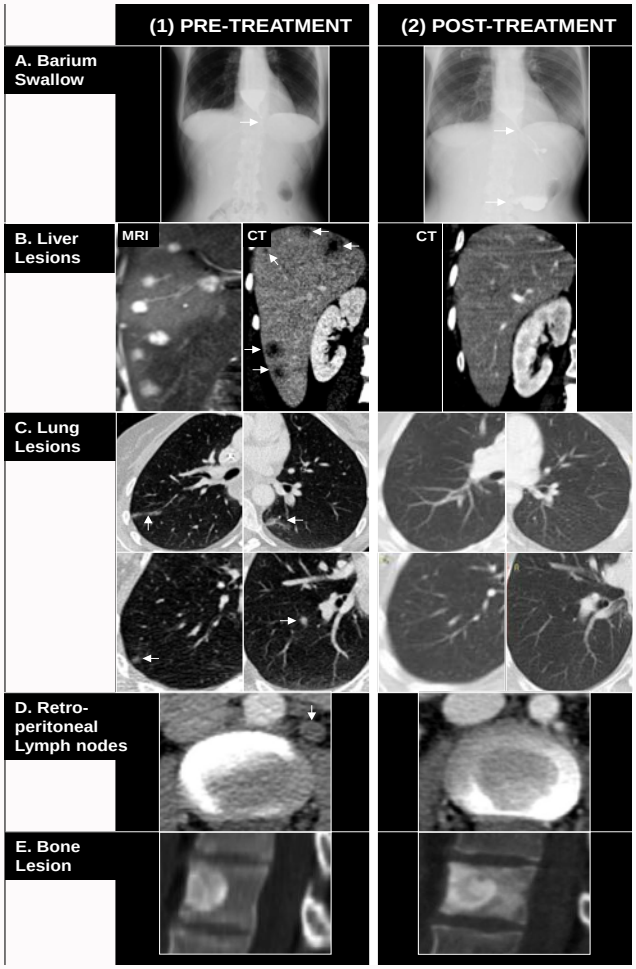

Figure 1: Locoregional Chemotherapy (LRC) and Oncolytic Virus (OV) therapy for a metastatic gastric tumor

A. Barium swallow: Functional obstruction (arrow) prior to treatment and relieved obstruction with barium passage distally to the stomach following treatment (arrow).

B. Liver: Pre-treatment MRI + CT images with multiple liver metastases, which were mostly resolved in the post-treatment CT.

C. Lung: Representative CT images of sub-centimeter lung nodules (up to 4) and subpleural infiltrates prior to treatment; post-treatment CT showed complete resolution. The pre- and post-treatment CT images were obtained on two different CT scanners with different acquisition parameters and image contrast.

D. Retroperitoneal lymph nodes: Enlarged retroperitoneal lymph nodes observed pretreatment were completely resolved after treatment, which aligns with the response to LRC and OV treatment.

E. Bone: MRI images of a solitary bone lesion in the L1 vertebra prior to treatment with post-treatment sclerosis, compatible with response to treatment.

Since the new medical center did not obtain regulatory approval for compassionate use of this experimental treatment, OV immunotherapy could not be continued. Three weeks later, she again

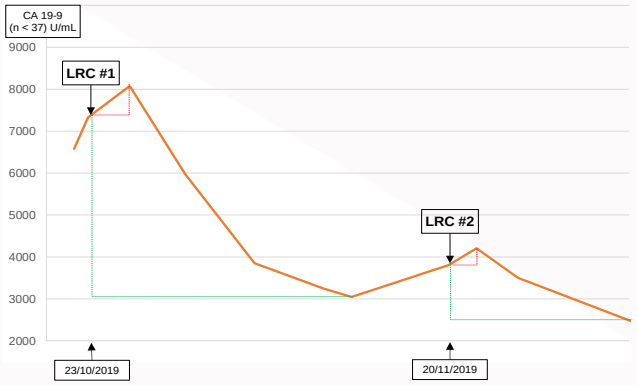

Figure 2: CA19-9 levels following Locoregional Chemotherapy (LRC) courses 1 and 2.
Following LRC #1 and LRC #2 the tumor marker showed the same pattern of response: After an initial short increased by 10% over ± 3 days from the pre-treatment baseline (dotted red line). Afterwards there was a decrease by ± 60% and ± 40% decrease over 18 or 12 days respectively (dotted green line).

experienced difficulties swallowing, and died (13-01-2020).

Discussion

The unique and synergistic combination of LRC and OV immunotherapy induced rapid and impressive clinical, laboratory and radiological responses in a palliative patient with significant disease progression after standard treatment. Despite the limitation of an irregular and inconsistent imaging surveillance routine, the imaging markers showed an unequivocally positive response to treatment. As shown in the post-treatment CT and by decreased tumor marker levels, LRC effectively eradicated metastases by exposing them to high local chemotherapy doses, which were rapidly washed out [10,11]. Venous escape of cytostatic agents has a desirable cytotoxic effect on metastases, since they follow the anatomical vascular route of the initial metastatic spread from the primary tumor. Brief loco-regional exposure to high-dose chemotherapy also has considerably fewer systemic side effects than systemic chemotherapy. The initially increased CA 19-9 levels may reflect the presence of destroyed tumor metabolites after LRC, while the continuous decrease in levels over the following 12 to 18 days may reflect ongoing tumor destruction. Introducing LRC at an earlier stage inpatient, who do not have a meaningful response to standard chemotherapy, might improve its efficacy while maintaining tolerability.

The targeted anti-tumor effect of OVs selectively triggers immune-mediated apoptotic processes in tumor cells, while mostly sparing normal cells. OVs can be administered intratumorally and induce favorable anti-tumor immunity to systemically fight metastatic tumor cells. Thus, OV is a promising therapeutic modality, with improved efficacy upon intratumoral administration [12]. Despite the promising reduction in tumor marker levels, our patient could not swallow after two cycles of LRC, possibly due to the effect of LRC on the external component of the primary mass. Furthermore, previous radiation at the GEJ might have reduced the immediate effect of LRC. In contrast, intra-tumoral injection of OV was followed by immediate clinical and radiological improvement in esophageal patency, which had been fully obstructed for 3 months due to tumor compression.

In the presented case of a refractory tumor, combination of LRC and intratumor-injected OV as orthogonal modalities appeared to have a synergistic effect, impacting the external part of the tumor and its metastatic spread as well as local and intraluminal tumor components. While systemic chemotherapy weakens the immune system, LRC offers more intensive tumor killing with significantly less immunosuppression and improved tolerability due to limited systemic exposure. Indeed, following maximal chemotherapy, our patient eventually suffered from compromised immunity, manifested by prolonged neutropenia, heartburn for >12 months, and tumor growth during pregnancy, a physiological state in which the mother's immune status is suppressed [13]. In contrast, OVs induce oncolytic effects at the cellular level, including cell-based immune responses and cytokine release. These effects enhance the local cytolytic response, which is critical for successful systemic cancer immunotherapy. This promising approach is expected to eradicate minimal residual disease over time.

Future integration of LRC and OV should be considered based on clinical criteria. While standard chemotherapy may be effective in reducing tumor growth and size, significant side effects (e.g., neutropenia) can delay initiation of LRC and OV, as seen in our patient. Thus, once standard chemotherapy fails to induce a satisfactory therapeutic response or becomes poorly tolerated, immediate introduction of combined LRC and OV should be considered to maximize their therapeutic potential.

Future protocols should employ appropriate monitoring methods for patients undergoing LRC and OV, including blood tests to assess tumor shrinkage, immune responses and virological parameters.

Specific radiological evaluation of the tumor size and inflammatory response tends to differ from routine cancer assessment criteria of response to treatment [14]. Tumor microenvironments have unique immunological and inflammatory characteristics, which can be accessed through imaging biomarkers. A consistent surveillance imaging protocol with clinical-immunological correlation may provide a better understanding of the tumor microenvironment and may uncover predictive markers for prognosis.

Rationalizing the roles of various therapeutic modalities and integrating the promising approaches of LRC and OV in future clinical trials might significantly improve clinical outcomes.

Author Contributions

BG reviewed all data and prepared the manuscript; JSR reviewed and interpreted all radiological data and prepared them for the manuscript; YP, and RE contributed to the preparation of the manuscript and review of the literature; Treatments were planned, coordinated and performed by KA (LRC) and AT (OV).

Funding

The paper was written with the financial assistance of Rapo Yerape Ltd.

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