Beyond the Beyond: A Case of an Extraordinary Response to Multiple Lines of Therapy in a de novo Metastatic HER2-Negative Gastric Cancer Patient

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Abstract
Background: Gastric cancer is the fourth cause of cancer-related death in Europe and the prognosis of these patients remains dismal. It has been demonstrated that chemotherapy improved survival compared with best supportive care and recently, subsequent lines of therapy, also with new drugs, obtained positive results. Summary: We present the case of a patient diagnosed with a de novo metastatic gastric cancer who experienced an extraordinary long response to multiple lines of chemotherapy (FOLFOX6, paclitaxel plus ramucirumab, FOLFIRI, rechallenge with FOLFOX6). Key Message: Gastric cancer therapy should be considered as the result of a strategy based on the patient’s condition, and tolerance and response to various therapies. The emerging evidence of the role of subsequent lines of therapy, along with the recognition of the pivotal role of nutritional support and the availability of new drugs, should help clinicians in the management of patients with gastric cancer. Practical Implications: We propose a practical therapeutic algorithm in order to help clinicians who deal with patients with gastric cancer.
Introduction

Gastric cancer is the fourth cause of cancer-related death in Europe [1]. The vast majority of gastric cancer cases are diagnosed at an advanced stage or develop a recurrence after surgery. Although chemotherapy improves survival compared with best supportive care, the prognosis of these patients remains dismal, with median survival approaching 11 months. The addition of trastuzumab to first-line chemotherapy in patients with HER2-positive gastric cancer represents a cornerstone in the management of metastatic disease, with a median survival that has exceeded 1 year for the first time [2]. Furthermore, the superiority of second-line chemotherapy over best supportive care (or active symptom control) has been recently established by randomized trials and meta-analyses [3–6]. Analogously, the discovery of the pivotal role of vascular endothelial growth factor receptor 2 (VEGFR2) in the pathogenesis of gastric cancer paved the way for the development of ramucirumab (a monoclonal antibody that targets VEGFR2) which, alone or in combination with paclitaxel, represents the actual standard of care in second-line treatment of gastric cancer [7, 8].

In this rapidly evolving clinical scenario, it has emerged that the management of patients with gastric cancer should be considered a sort of therapeutic journey rather than the result of extemporaneous choices.

To provide prognostic and predictive information on gastric cancer, beyond histological classification (WHO and Lauren’s classifications), anatomical division (Borrmann and Siewert and Stain classifications), and extent of the disease, in recent years studies on molecular characterization tried to obtain other important information. In 2013 Lei et al. [9] described three subtypes of gastric adenocarcinoma based on mRNA analyses: proliferative, metabolic, and mesenchymal subtypes. A year later, as a part of The Cancer Genome Atlas project (TCGA), Bass et al. [10] divided gastric cancer into four subtypes: tumors positive for Epstein-Barr virus (EBV) (9%), microsatellite unstable tumors (MSI) (22%), genomically stable (GS) tumors (20%), and tumors with chromosomal instability (CIN) (50%). In the meantime, the Asian Cancer Research Group (ACRG) proposed the classification of gastric cancer in the mesenchymal subgroup with hall-marks of epithelial-to-mesenchymal transition (MSS/EMT), microsatellite instability subgroup (MSI), microsatellite stable TP53-positive tumors (MSS/TP53+, somehow overlapping with EBV type by TCGA), and microsatellite stable TP53-negative tumors (MSS/TP53−, partly similar to CIN by TCGA) [11].

We present a case of a patient with a de novo metastatic gastric adenocarcinoma who achieved an outstanding survival with the integration of a sequence of multiple lines of chemotherapy and appropriate supportive care.

Case Description

In December 2013, due to weight loss and epigastric pain, a 71-year-old male, with an ECOG performance status of 0, underwent a computer tomography (CT) scan which revealed multiple bilobar liver metastases, enlarged abdominal lymph nodes, and ascites. A gastroscopy demonstrated an ulcerated mass of the gastric corpus with a histological diagnosis of an intestinal-type adenocarcinoma. The immunohistochemical assay for HER2 was negative (score of 0). He presented an increase in tumor markers (Fig. 1).

In January 2014 he started chemotherapy with FOLFOX6 at the standard dose, achieving a partial response of liver metastases and lymph nodes along with a biochemical response (Fig. 1). At the same time, an early integration of home-based palliative care was provided. For peripheral neuropathy, after 10 cycles we decided to stop oxaliplatin and continued with 5-FU + FA (de Gramont regimen) from June 2014 to January 2016 (38 cycles). The patient has maintained an ECOG performance status of 0.

In February 2016 the CT scan showed a progression of liver metastases and the patient started a second-line treatment with paclitaxel; during the second cycle ramucirumab was added, achieving disease stabilization.
In September 2016, due to hepatic and peritoneal progression of the disease, the patient underwent a third-line treatment with 6 cycles of modified FOLFIRI, achieving a partial response, and continued a maintenance therapy with capecitabine until the end of February 2017.

At this time, the patient presented a marked clinical deterioration because of an intestinal subocclusion which required hospitalization for around 10 days. The CT carried out on March 2017 showed pleural effusion, considerable ascites, and an increase of liver lesions and abdominal lymph nodes. After counseling, he started parenteral nutrition, underwent paracentesis, and received a rechallenge therapy with modified FOLFOX6. The first cycle was done without bolus of 5-FU and at 50% of the standard dose, but soon after his condition improved. He stopped parenteral nutrition support because of a complete recovery of oral feeding after some months and returned to an ECOG performance status of 0. After 6 cycles, the CT scan showed a partial response of the disease with a decrease of peritoneal carcinomatosis and lymph nodes and stability of liver lesions. He then started a new maintenance therapy with the de Gramont regimen. As of today, the patient is still alive and in good condition.

Molecular Characterization

We performed some analyses to characterize the molecular profile of this long chemotherapy-responding disease. The results are reported in Table 1. We exclude this tumor at least from EBV-related cancer and MSI subtype due to no cell positive for EBV and normal

Fig. 1. Time line with the sequence of therapies, radiological evaluations, and levels of serum markers. The image shows the correspondence between CEA and CA 19-9 trend and radiological response or progression during therapy. From top to bottom: line of therapies and drugs administrated, representative images from CT scanning at important moments of the disease, and trend of serum levels of CEA (ng/mL) and CA 19-9 (U/mL). PR, partial response, SD, stable disease; PD, progressive disease; nv, normal value.
expression of MMR protein, respectively. The immunohistochemical assay showed no reaction for PD-L1 antigen. Molecular analysis highlighted no mutation in different genes codifying both receptor and intracellular transduction proteins important for cell survival and proliferation. This makes us hypothesize that the growth of this tumor is not subject to one of the most frequent molecular alterations researched.

**Conclusions**

Gastric cancer therapy should not be considered as a single choice at the time of the diagnosis, but rather the result of a strategy based on the patient’s condition, and tolerance and response to previous therapies. In other contexts, such as colorectal cancer, it has been established that exposure to all active drugs can maximize the results in terms of survival [12]. Our patients received four lines of chemotherapy. In gastric cancer, while several clinical trials recently demonstrated the impact of second-line therapy, the role of subsequent lines remains questionable. Recently apatinib, a novel VEGFR2 tyrosine kinase inhibitor, has demonstrated a survival advantage over placebo in patients with gastric cancer treated with at least two lines of chemotherapy [13]. Furthermore, a recently published real-world case series showed that selected patients with advanced gastric cancer (in particular those who had a good response to previous lines of therapy) can benefit from a third-line treatment [14].

Moreover, in this case the treatment was characterized by phases of induction (with the aim of maximizing the response), which were alternated with phases of de-escalation in a maintenance therapy with a less toxic drug (with the aim of preserving the patient’s quality of life). Although maintenance therapy has never proved to be effective in gastric cancer, this approach that mimics the “continuum of care” of colorectal cancer, in which the treatment is tailored to the clinical setting and the lines of therapy are blurred rather than discrete, deserves further exploration [15].

Another interesting aspect emerging from our case is the opportunity to reuse a drug which has already proven to be effective in previous lines. The biological basis of the rechallenge lies in the fact that the genetic and epigenetic changes that underlie the evolution of a

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**Table 1. Molecular characterization**

| Analysis                               | Results                                      |
|----------------------------------------|----------------------------------------------|
| MMR protein IHC                        | normal expression                            |
| PD-L1 IHC                              | negative                                     |
| ALK IHC                                | negative                                     |
| Epstein-Barr virus (EBER) PNA probe**   | negative                                     |
| EGFR (exons 18, 19, 20, 21)            | wt                                           |
| K-RAS (codons 12, 13, 59, 61, 117, 146) | wt                                           |
| N-RAS (codons 12, 13, 18, 59, 61, 117, 146) | wt   |
| BRAF (codons 466, 469, 594, 597, 600, 601) | wt   |
| PIK3CA (codons 38, 81, 88, 93, 108, 118, 354, 420, 539, 542, 545, 546, 549, 1021, 1025, 1043, 1047, 1049) | wt |
| ALK (codons 1156, 1196, 1269)           | wt                                           |
| DDR1 (codons 239, 638, 768)             | wt                                           |
| HER2 (codons 775, 776)                 | wt                                           |
| MAP2K1 (codons 56, 57, 67)              | wt                                           |
| RET (codon 918)                        | wt                                           |

**Table Note:**

**a** DAKO PNA ISH Detection Kit, Code Y5200. wt, wild type.
A polyclonal mass might resensitize it to a drug that has been discontinued, through the re-emergence of sensitive clones. While rechallenge of chemotherapy is an established strategy in colorectal cancer [16], no data have been published to the best of our knowledge about this strategy in gastric cancer treatment.

In addition, in our opinion, this case points out the role of serum CEA and CA 19-9, which seem to precede the clinicoradiological progression or response and prove to be useful tools for guiding clinical management and tailoring the patient’s follow-up (Fig. 1).

Furthermore, our case highlights the crucial role of nutritional counseling in patients with gastric cancer. Indeed, a vast amount of recently published data underlines how malnutrition of patients with gastric cancer both in the perioperative [17, 18] and palliative setting [19] can negatively impact on survival. Similarly, sarcopenia, a complex syndrome characterized by a generalized loss of skeletal muscle mass, is very common in patients with gastric cancer and represents a frequent cause of poor tolerance to medical and surgical treatments [20].

Waiting for the confirmation of the reproducibility of the TCGA classification in a broader population and in a daily practice setting, the absence of a “druggable” molecular target in this case makes the response to chemotherapy more considerable and beyond the expected.

In conclusion, our case of a patient with an extraordinary long survival despite a de novo metastatic gastric cancer points out the paradigm change in the management of this disease. The availability of new drugs and the emerging evidence of the role of subsequent lines of therapy, along with the recognition of the pivotal role of nutritional support, should help clinicians to go through the “long and windy road” of the management of patients with gastric cancer. Taking into account all these considerations, we propose a practical therapeutic algorithm in order to help clinicians who deal with patients with gastric cancer (Fig. 2).
Statement of Ethics

This article does not contain any studies with human or animal subjects performed by any of the authors.

Disclosure Statement

The authors declare that they have no conflict of interest related to the reported data. No funding was received for this study.

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