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A case report on the long-term survival of a patient with HER2-positive metastatic gastric adenocarcinoma and a short review of the current literature

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Summary The prognosis of patients with metastatic gastroesophageal cancer remains poor despite numerous promising clinical trials, and the clinical benefit of systemic therapies is under critical review. This case report of a patient with human epidermal growth factor receptor 2 (HER2)-positive metastatic gastric adenocarcinoma is an impulse for the importance of individual decision making and molecular guided treatment options.

Keywords Gastric cancer · Upper GI cancer · HER2 · Trastuzumab · Ramucirumab

Case presentation

A 70-year-old man presented with upper abdominal pain at the general practitioner in January of 2016. Medical history showed no prior illness or surgeries and, thus, no previous medication. In the physical examination, a reduced nutritional status with 65 kg at a height of 1.82 m became evident, but no other physical abnormalities could be detected. No dyspepsia or dysphagia was reported. An endoscopy showed a tumor in the antrum of the stomach with suspected covered perforation of the gastric wall.

The patient was then transferred to our hospital, and despite not being able to confirm the suspected perforation in a computed tomography, the patient was operated on shortly thereafter. A subtotal gastrectomy was performed. The histological report showed an already advanced HER2 (human epidermal growth factor receptor 2)-positive (ICH 3+) adenocarcinoma with lymph node as well as omental metastases (G3, pT3, L1, V0, Pn1, pN2a, pM1, R0). There was no visible residual disease. Adjuvant chemotherapy after the surgery was declined by the patient.

In September 2016, the patient presented with multiple liver and abdominal lymph node metastases and by then agreed to undergo chemotherapy. Six cycles of chemotherapy following the ToGA regimen (trastuzumab, cisplatin, capecitabine) were administered and partial remission was achieved. The patient experienced several chemotherapy-induced toxicities including infections, low white blood count, and acral erythema. Thus, chemotherapy was terminated after 6 cycles and a maintenance therapy with trastuzumab was established beginning in March 2017. This therapy was continued until October 2018, when restaging showed progression of lymph node metastases. Radiation therapy on the local lymph nodes together with oral capecitabine were administered between October and March 2019. Trastuzumab maintenance therapy was continued.

The next restaging in March 2019 showed a progressive disease with new pulmonal lesions and carcinomatosis peritonei. So far he had received 39 cycles of trastuzumab and it was surmised that the tumor might had lost its HER2-positivity. Furthermore, the patient presented with an ileus in April 2019, which had to be managed surgically with a colostomy. Due to this progress, the patient received second-line therapy with ramucirumab plus paclitaxel from April until October 2019, which induced a partial response after 6 cycles. Due to good response, maintenance therapy with ramucirumab was established in October 2019 until December 2019.

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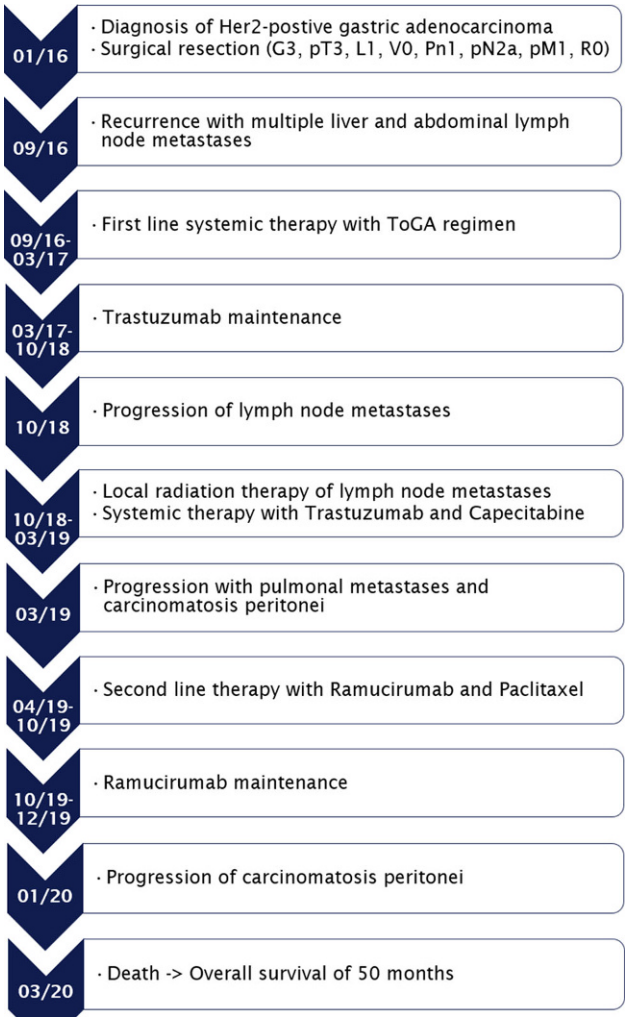

Fig. 1 Timeline of disease evolution

The patient wished to reverse the colostomy in January 2020. However, during the surgery a massive Carcinosis peritonei was detected and biopsied. Unfortunately no HER2 analysis was performed. The biopsy was microsatellite stable. Due to the progression of the peritoneal carcinomatosis, maintenance treatment with ramucirumab was discontinued after 2 months. A standard third-line treatment with trifluridin and tipiracil was discussed with the patient. After surgery the status of the patient deteriorated quickly and he died in March 2020 in the palliative care unit due to rapid tumor progression. The overall survival (OS) was 50 months (Fig. 1).

Critical discussion and review of the literature

This case report of a patient with initially metastatic, HER2-positive gastric adenocarcinoma attends several important steps concerning treatment options.

Surgery

First, the patient received a subtotal gastrectomy due to the suspected perforation and the lack of evidence of advanced disease in the computed tomography. Even though it was evident once the surgery began that he was in a locally advanced state, the gastrectomy was performed to treat the suspected perforation. Without the suspected perforation the treatment of choice would have been a perioperative chemotherapy regimen, with a neoadjuvant regimen of FLOT (leucovarin, 5-fluorouracil, oxaliplatin, and docetaxel). This treatment regimen represents a quite novel treatment option, which showed promising results in a first-line perioperative setting [1]. This regimen can be considered as first-line therapy for patients with an excellent performance status. Furthermore, there were several trials to evaluate the role of HER2-targeted therapies in a first-line resectable setting of gastroesophageal adenocarcinoma; however, so far there have been no practice-changing results [2, 3].

Perioperative systemic therapy

The patient refused even adjuvant chemotherapy and only a few months later developed rapid recurrence with liver and lymph node metastases. This underlines the importance of adjuvant treatment particularly in advanced settings [4].

Palliative systemic therapy—first line

Due to the palliative state of the HER2-positive metastatic, gastric adenocarcinoma, a treatment according to the ToGA trial was administered [5]. Although this regimen provides a widely prolonged survival, the toxicities often lead to severe adverse events. Thus, several trials try to exchange cisplatin with oxaliplatin, seen as it has a more favorable toxicity profile [6]. However, so far no new treatment options for this setting are available. Also, other treatment strategies for HER2-positive gastric cancer have so far failed to improve the overall survival (OS) [7, 8].

After 6 cycles of therapy partial remission and an excellent performance score could be achieved; thus, trastuzumab maintenance therapy was established according to recently published observations [9–11].

Radiation therapy

This maintenance was continued for 7 months, until there was a minor progression in lymph nodes metastases; however, stable disease concerning the liver metastases was evident. Thus, it was decided to treat the localized lymph node metastasis with radiotherapy and to expand the maintenance therapy with capecitabine. Radiation therapy of localized lymph

node metastases is known to be effective as palliative treatment and to prolong OS [12, 13].

Palliative systemic therapy—second line

After 39 cycles of trastuzumab treatment, there was a progression with expansion of known liver and lymph node metastases as well as development of pulmonal metastases. Although trastuzumab proved to be very effective in our patient, we decided not to continue this treatment beyond progression. This decision was based on the results of a phase II study comparing the combination of paclitaxel beyond progression with trastuzumab versus paclitaxel alone, which showed that there was no benefit of combination therapy concerning OS [14]. Furthermore, other trials that targeted HER2 in a second-line strategy also failed to improve OS [15, 16]. It is surmised that this effect might be due to the loss of HER2 after first-line treatment [17].

Thus, we decided to further manage this patient as a HER2-negative case and applied the standard second-line chemotherapy with ramucirumab and paclitaxel [18]. A recent subgroup analysis of the initial trial also demonstrated efficacy benefits of this regimen after trastuzumab-based treatment [19]. However, the European Society of Medical Oncology—Magnitude of Clinical Benefit Scale (ESMO-MCBS), a score which indicates the substantial magnitude of clinical benefit of particular novel treatment options in oncology, is only 2 for ramucirumab and paclitaxel [20]. Thus, the clinical benefit for the patient might be minimal and that is why this regimen is critically viewed and widely discussed as a second-line option. However, our patient had a subjective benefit and good response throughout this therapy.

Palliative systemic therapy—third line

As a third line, we discussed to establish a therapy with trifluridin and tipiracil. This treatment option was published in 2018 and showed promising results on OS and quality of life when compared to placebo [21, 22]. Unfortunately, our patient died before this therapy regimen could be administered. The rapid deterioration after the surgery to reverse the colostomy was associated with rapid tumor progression. The cause for this rapid progression is not evident and might be due to the discontinuation of the antiangiogenic drug ramucirumab, the surgery itself [23], late knowledge of carcinomatosis due to low detection rates in CT scans [24] as well as other various unknown reasons.

Survival and prognosis

Despite the success of modern chemotherapy, patients with metastatic gastric cancer continue to have a dismal outcome. The 5-year relative survival for metastatic gastric cancer is 5.5% [25]. The median OS from therapy initiation until death was 13.9 months in HER2-positive patients in the ToGA trial. As mentioned above, this outcome represented a major breakthrough in modern oncology [26]. However, whether HER2-positivity is an independent prognostic marker is controversially discussed [27].

Furthermore, despite the fact that patients with peritoneal carcinomatosis with no measurable disease are known to have a significantly longer survival than that of patients with measurable disease (18.0 vs. 11.6 months), the median survival is still poor [28].

With regard to this data, the survival of our patient was exceptional. This might be due to the good performance status as well as the long treatment responses to first- and second-line therapy. Furthermore, individual treatment decisions which are made in interdisciplinary tumor boards might have contributed to this exceptional survival outcome as well. In addition, a favorable intrinsic biologic behavior of the tumor due to unknown mutations must also be considered. This underlines the importance of new prospective trials to further characterize and analyze gastric cancer cells.

Further considerations

Another important issue to discuss is the microsatellite instability (MSI). In 2017, the checkpoint inhibitor pembrolizumab was approved by the US Food and Drug Administration for the treatment of unresectable or metastatic MSI high solid tumors without any satisfactory alternative treatment options after at least one prior treatment [29]. Thus, pembrolizumab is a valid second and further line option for metastatic gastroesophageal tumors, which are MSI high. Unfortunately, the analysis of our patient's tumor showed microsatellite stability and, thus, this treatment option was not possible.

Concerning future directions, novel anti-HER2 approaches and combinations are gaining attention. A recent phase II trial showed promising results with the antibody-drug conjugate trastuzumab deruxtecan as a third and further line strategy for patients with HER2-positive advanced gastric cancer [30]. This option is expected to be practice-changing within the next couple of years.

Another potential breakthrough was recently published in June 2020 and shows that pembrolizumab combined with trastuzumab and chemotherapy has promising activity in HER2-positive metastatic esophagogastric cancer in a first-line setting [31].

Conclusion

Biomarkers such as HER2 and MSI are of high clinical interest, treatment relevant and might have prognostic impact on the OS of gastroesophageal adenocarcinoma patients. In conclusion, there is a clear first-line standard for those patients. However, second and fur-

ther line treatment options are scarce and the clinical benefit of such strategies is under critical discussion. New treatment options are desperately needed and there are several ongoing trials, which are promising.

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