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Case and Review

Cure Is Possible: Extensively Metastatic HER2-Positive Gastric Carcinoma with 5 years of Complete Remission after Therapy with the FLOT Regimen and Trastuzumab

Sebastian Schade[a] Ute Koenig[b] Ardian Mekolli[b] Jochen Gaedcke[c] Albrecht Neesse[b] Johanna Reinecke[b] Marius Brunner[b] Ali Seif Amir Hosseini[d] Julia Kitz[e] Philipp Stroebel[e] Joachim Lotz[d] Michael Ghadimi[c] Volker Ellenrieder[b] Alexander Koenig[b]

[a]Department of Clinical Neurophysiology, University Medical Center, Goettingen, Germany; [b]Department of Gastroenterology and Gastrointestinal Oncology, University Medical Center, Goettingen, Germany; [c]Department of General-, Visceral- and Pediatric Surgery, University Medical Center, Goettingen, Germany; [d]Department of Diagnostic and Interventional Radiology, University Medical Center, Goettingen, Germany; [e]Institute of Pathology, University Medical Center, Goettingen, Germany

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Advanced gastric cancer · HER2/neu · Trastuzumab · Treatment strategies

Abstract
Gastric cancer (GC) represents one of the most fatal neoplasms in gastrointestinal oncology and affected patients can only hope for cure in limited disease. In a metastatic situation however, patients have a worse prognosis finally resulting in cancer-related death. Some improvements were made by using intensified chemotherapy such as the FLOT protocol (5-FU, leucovorin, oxaliplatin and docetaxel). However, a breakthrough in the treatment of advanced GC has been achieved by pre-therapeutical tumor analysis for potentially targetable alterations. Microsatellite instability, PD-L1 expression, Epstein Barr virus, and human epidermal growth factor receptor-2 (HER2) overexpression or amplification are the most beneficial targets, if addressed, can prolong survival in a palliative situation. Whether the combination of these

S.S. and U.K. share first authorship.

Correspondence to:
Ute Koenig, ute.koenig@googlemail.com

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targeted therapeutics with chemotherapy can bring long-term survival or even a chance of cure in a metastatic situation is not clear. Here, we report the case of a 30-year-old man with GC and extensive metastases who was cured by anti-HER2 antibody Trastuzumab combined with the FLOT regime. Initial staging showed an exophytic Siewert type III tumor and extensive hepatic metastases. Histology resulted in gastric adenocarcinoma with HER2 overexpression (2+, FISH positive). Twelve courses of chemotherapy comprising Trastuzumab and FLOT were administered. After treatment, the extensive liver metastases had disappeared with no evidence of residual tumor growth on the CT scans. Monotherapy of Trastuzumab was continued until gastrectomy with D2 lymph node dissection and probing of liver tissue, which revealed no residual tumor cells. Five years after surgery, there is continued complete remission. In conclusion, Trastuzumab in combination with FLOT may have curative potential even for metastatic stages of HER-2-positive GC.

Introduction

The median overall survival of patients with advanced gastric cancer (GC) treated with chemotherapy is about 12 months (4 months without chemotherapy, respectively) [1]. Even in young patients (<40 years), the 5-year overall survival of stage IV GC in western countries is negligible [2]. About 9–38% of all GCs show an overexpression of the human epidermal growth factor receptor-2 (HER2), which might play a prognostic role for a more aggressive disease and a worse outcome, although this issue remains unclear with so far contradicting results in different studies [3–5]. Despite this controversy, the HER2 status is clinically relevant today, since several phase II trials [6, 7] and the large phase III ToGA trial [8] proved a significant benefit from treatment with trastuzumab (Tmab), a humanized monoclonal antibody targeting HER2. Nevertheless, there has been a growing concern about secondary resistance to Tmab, its prognostic factors and strategies how to overcome this obstacle [9].

We present a case of an advanced cancer of the gastroesophageal junction (GEJC) with extensive liver metastases that showed complete pathological response and a long-term tumor-free survival of more than 5 years after treatment with Tmab in combination with FLOT. Afterwards, while reviewing the literature, we discuss specifically intriguing aspects of this impressive clinical course that might be worthwhile considering when assessing treatment response to targeted immunotherapy in advanced GC.

Case report/Case Presentation

A previously healthy 30-year-old Caucasian male presented with a 3-week history of abdominal pain, loss of appetite, fatigue, and abdominal distension. Symptoms were increased postprandially, but there was no weight loss reported (176 cm, 67 kg, BMI 21.6). He reported night sweats. The patient had not taken any medication, there were no known allergies, and he was a former smoker. Family history comprised no malignancies. Clinical investigation revealed no pathologic findings but hepatomegaly with epigastric tenderness. Abdominal ultrasound showed a massively enlarged liver with suspected multiple metastases, small amounts of perihepatic ascites and enlarged retroperitoneal lymph nodes. Gastroscopy revealed exophytic Siewert type III tumor growth (Fig. 1a). There were normal findings in colonoscopy. A CT scan confirmed multiple liver metastases (Fig. 1b), enlarged retroperitoneal lymph nodes and ascites, as well as a thickening of the lower esophageal wall. There was no evidence of lung metastases. A biopsy of the liver metastases resulted in adenocarcinoma of the upper GI tract.

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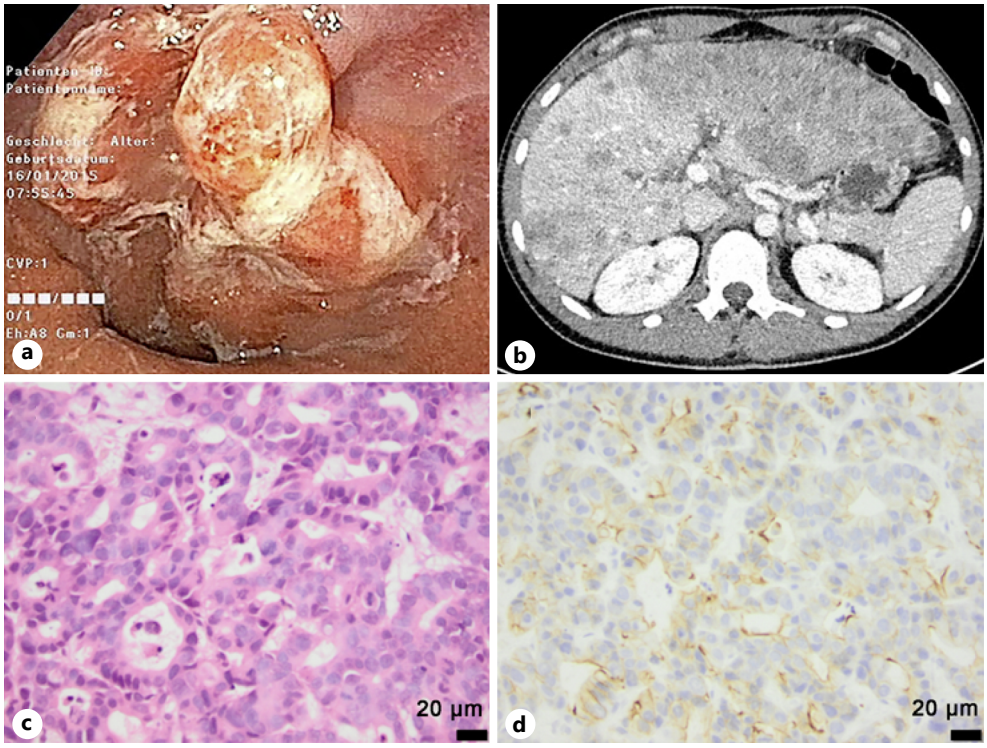

Fig. 1. a Endoscopic findings, January 2015: Siewert type III GEJC. **b** CT scan at diagnosis, January 2015: multiple liver metastases and enlarged retroperitoneal lymph nodes. **c** Pathological findings: gastric adenocarcinoma G2, hematoxylin/eosin staining, at a 20-fold magnification. **d** Overexpression of HER2/neu protein (2+), anti-HER2 immunostain (DAKO A0485), at a 20-fold magnification.

Histology resulted in moderately differentiated gastric adenocarcinoma (G2) strongly overexpressing HER2/neu protein (2+) (Fig. 1c, d).

According to recently published data [10], the patient was treated with Trastuzumab (4 mg/kg) in combination with the FLOT regimen (5-FU 2,400 mg/m^2 civ 24 h, Leucovorine 200 mg/m^2, Oxaliplatin 85 mg/m^2, Docetaxel 50 mg/m^2 biweekly) for 6 cycles. Before treatment and during the first 2 cycles of therapy, the patient developed tumor lysis syndrome and was treated as an inpatient, receiving additional i.v. fluids and rasburicase, without persisting kidney damage. The following cycles were administered in the outpatient chemotherapy unit.

The patient had an extraordinarily strong skin reaction with erythema and partial eruptive eczema of the face, feet, and hands up to the armpits, associated with paronychia and onycholysis (Fig. 2a,b). In addition to pericardial effusions, he developed ascites and pleural effusions, both of which had to be drained repeatedly (Fig. 2c, d). Cytologic assessment of the ascites and pleural effusions samples was repeatedly negative for tumor cells, which suggests docetaxel or trastuzumab as possible causes, or impaired liver function as a side effect of chemotherapy or intrahepatic remodeling after tumor lysis of the extensive hepatic metastases. After 6 cycles of therapy, a CT scan revealed tumor response in the liver as well as the lymph nodes and esophageal wall thickening (Fig. 3a). Combination therapy of trastuzumab and FLOT was continued, FLOT doses were reduced to 75% due to hematotoxicity and peripheral polyneuropathy. Filgrastim 30 Mio IE s.c. was administered on days 4–6. After 6 additional cycles of therapy, CT staging and gastroscopy showed a complete remission (Fig. 3b). The tumor marker carcinoembryonic antigen normalized after initially elevated levels (51.3 µg/L).

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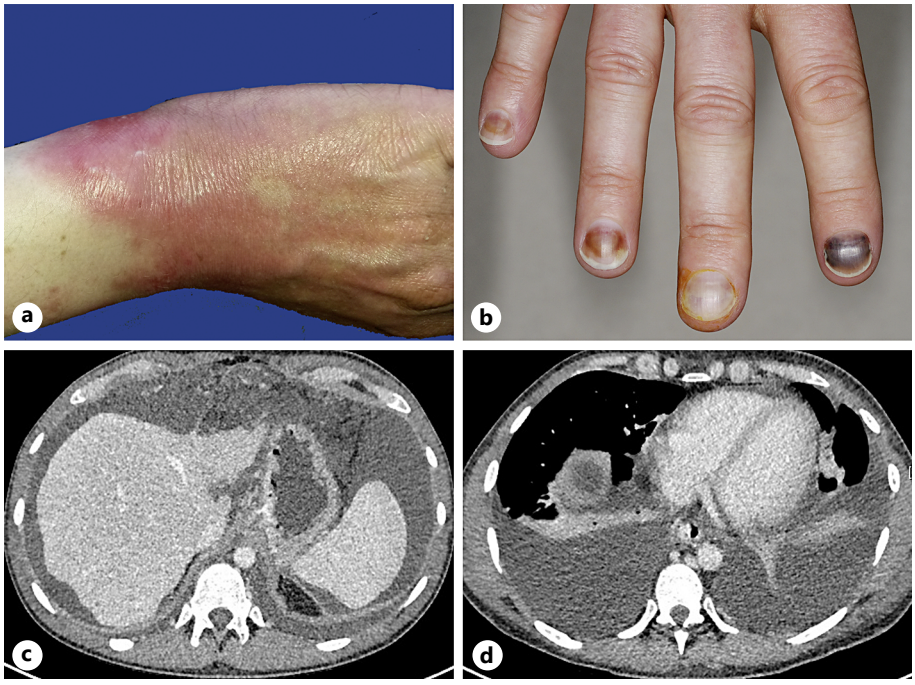

Fig. 2. a Grade 3–4 skin reaction with erythema, left arm. **b** Paronychia and onycholysis of the left hand. **c** CT scan: Ascites, July 2015. **c** CT scan: Pleural effusions, July 2015.

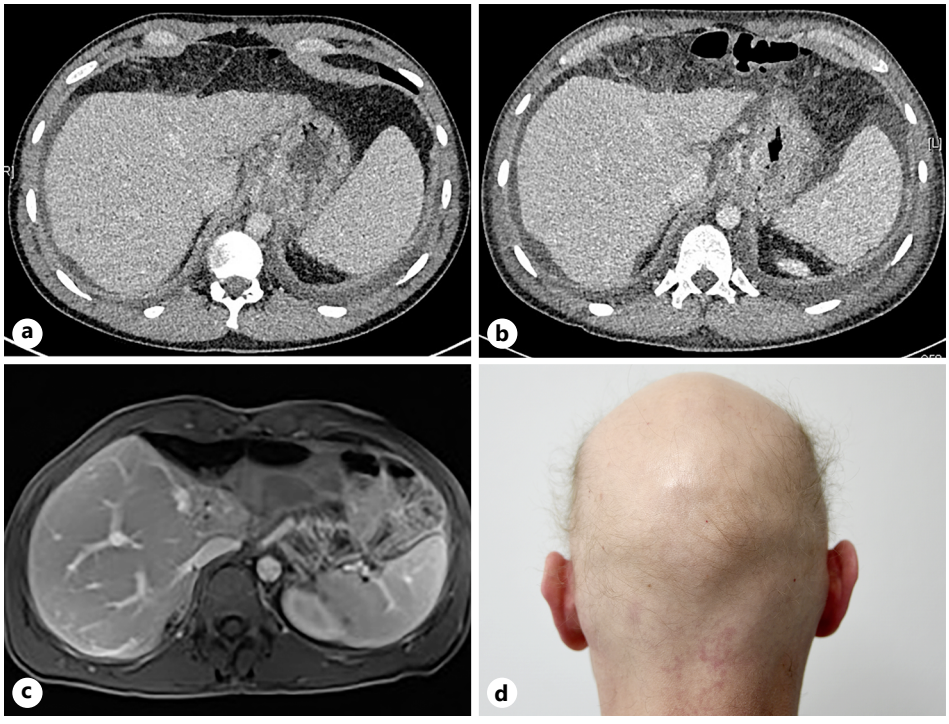

Fig. 3. a CT scan after 6 cycles of FLOT and Trastuzumab, April 2015: partial response of liver metastases and lymph nodes. **b** CT scan after 12 cycles of FLOT and Trastuzumab, July 2015: Complete Remission of liver metastases and lymph nodes. **c** MRI scan April 2020, contrast-enhanced by gadolinium (Primovist®), no evidence of liver metastases. **d** Persistent alopecia 5 years after completion of chemotherapy.

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Pleural effusions and ascites were persistent, but decreased slightly. Trastuzumab was continued as a monotherapy for 4 more cycles. Surgery with gastrectomy and liver biopsy was performed 1 year after diagnosis. There was no evidence of macroscopically visible tumor remnants, histology showed no residual tumor cells neither in the resected stomach and lymph nodes nor in the liver biopsy. Due to pathologically complete response, no adjuvant chemotherapy was administered. CT and MRI scans were performed 12-weekly within the first year, then every 6 months, and after 3 years annually. Five years after resection (and 6 years after initial diagnosis), there is continued complete remission on imaging and normal carcinoembryonic antigen-levels (Fig. 3c). Pleural and pericardial effusions and ascites have completely resolved. The left liver lobe has retracted due to thrombosis of the left portal vein, while the right lobe of the liver seems to have regenerated, initially with a rather fibrotic aspect, gradually decreasing over time.

The patient has still a nearly complete alopecia (Fig. 3d), brittleness of the nails, mild peripheral neuropathy, and mild common side effects due to gastrectomy. Annual echocardiography showed no signs of impaired cardiac function (LVEF >55%) in the aftermath of trastuzumab therapy.

Discussion

We illustrate the first reported case of pathological complete remission and long-term tumor-free survival after neoadjuvant chemotherapy with a trastuzumab-containing regimen (FLOT + Tmab) in a patient with extensive hepatic metastases in advanced adenocarcinoma of the GEJC, overexpressing HER2. This is in line with several reports of pathological complete or near-complete remission in locally (M = 0) advanced GC [11, 12].

Since the first promising case reports [10] in metastatic GC, especially concerning hepatic metastases, results have been contradicting. Preliminary data of a phase II study with docetaxel, oxaliplatin, 5-FU, and Tmab as first-line therapy showed feasibility and efficacy, but clinical complete response was reached in only 2 (out of 15) patients and mean overall survival was 19.4 months [13]. The prospective phase II AIO-FLOT3-trial showed that patients with limited metastatic GC or GEJC benefit from neoadjuvant chemotherapy under the FLOT regime followed by surgical resection [14]. Most notably, subgroup analyses revealed that patients with liver metastases showed a less favorable survival, leading the authors to the conclusion to exclude patients with potentially nonresectable liver metastasis from further trials. Under this rationale, our patient would have been excluded. Therefore, we would like to highlight aspects of our case that might be helpful in defining prognostic characteristics for targeted therapy with Tmab even in patients with advanced GC or GEJC.

With 30 years of age, our patient was young at disease onset, had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0, and suffered from no comorbidities. A good ECOG performance status has been beneficial in several studies [15–17]. Median age in most studies is well above 60. Young adults with GC are more likely to present with metastases (stage IV) and, therefore, are associated with a poorer prognosis [2]. Some authors consider GC in younger patients as a different clinical entity, but most studies show no significant difference in cancer-related survival compared to older patients, especially in advanced GC [18–21]. Nevertheless, a better benefit for young patients (although generously defined as 65–70) has been observed in a sub-analysis of the FLOT65 + study with the docetaxel-including 3-drug combination FLOT, as has been used in our case. After introduction of Tmab for HER2 positive tumors, further data have been reported on a better outcome for young patients [16].

Our patient had a primary tumor of the gastroesophageal junction of the intestinal type [22] with unresectable liver metastases and lymph nodes. While GEJC epidemiologically is on the rise, typically diffuse-type carcinomas are more frequent in younger age [2, 23, 24].

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This issue might be important since in consequence, the poor prognosis of advanced GC or GEJC in young patients [14] might be related to some extent to this pathological subtype. At least, it has been shown that in a perioperative setting, there seems to be an increased pathological response under treatment with (docetaxel-based) FLOT for intestinal type carcinomas [25]. Furthermore, HER2 overexpression was significantly higher in GEJC as compared to other locations [26], and it has a high correlation with the presence of the intestinal histological type [27]. Since the intestinal type has been associated with hematogenous metastasis [28], this might be an explaining link to the positive correlation between HER2 overexpression and hepatic metastases [28, 29]. Additionally, several studies have found a high concordance rate of HER2 expression between primary and secondary sites, which suggests that generally HER2 status remains stable during the metastatic process [9, 30]. Some authors even speculate that GC liver metastases are a unique clinical entity sharing the same characteristics [31], like sensitivity to HER2-targeting drugs. Hence, Tmab could reverse the poor outcome of HER2-positive GC in these young patients, particularly with liver metastases [29, 32].

HER2 overexpression itself has been associated with high-grade tumors, advanced stages, and a higher GC-specific mortality, therefore being an independent unfavorable variable [26]. Nevertheless, the prognostic value of HER2 positivity in advanced GC is a controversial issue with so far contradicting results in different studies [4]. It has been proposed that HER2 homogeneity has a worse prognosis compared to HER2 heterogeneity and Tmab might be more effective in patients with HER2 homogeneity, respectively [33]. The underlying pathomechanism of secondary resistance to Tmab is not clear yet [9]. One possible explanation could be the loss of HER2 positivity during therapy [34]. Cell line studies show diverse synergistic, additive, or antagonistic effects of different chemotherapeutic agents in combination with Tmab [35–37], so that individualized treatment regimens might be needed for different patients. Furthermore, it has been hypothesized that target molecules of just 1 receptor may be neutralized or attenuated by other pathways; therefore, combined targeted therapies have been proposed [38]. Prognostic factors and strategies of overcoming resistance to treatment with Tmab are urgently needed. Whether the formulation of new anti-HER2 strategies such as linking antibodies with conventional chemotherapeutic drugs like trastuzumab deruxtecan will be able to overcome resistance towards HER2 targeted therapy and improve curative potential of this therapeutic strategy, as suggested by latest clinical trials [39], has to be shown in future clinical investigations.

Additionally, we would like to emphasize two remarkable aspects of the clinical course of our patient. First, the patient showed a severe tumor lysis syndrome at the beginning of the treatment, which might be helpful in evaluating efficacy of the treatment regimen. Second, we observed an impressive skin reaction, including all extremities, the face as well as various sites of mucosa. Additionally, nearly complete alopecia is persistent up to the present time, more than 5 years after therapy (Fig. 3d). Taken together with the aseptic polyserositis (pleural, pericardial, peritoneal effusions) this might be a sign of an excessive, prognostically favorable immune reaction due to Tmab application.

Our case illustrates the first reported case of pathological complete response and long-term survival after neoadjuvant chemotherapy with a trastuzumab-containing regimen in a patient with extensively hepatic metastasized advanced GEJC overexpressing HER2. Special features of the case might be helpful as clues for further insight to prognostic factors of treatment response to Tmab-containing chemotherapy regimens.

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Statement of Ethics

Written informed consent according to the Declaration of Helsinki was obtained from the patient for publication of this case report and any accompanying images. This study protocol was reviewed and the need for approval was waived by the Ethikkommission der Universitätsmedizin Göttingen.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

S.S., U.K., and A.K. developed the concept of the report, conducted the literature search, and reviewed the retrieved data. S.S., U.K., V.E., and A.K. wrote the manuscript. All authors contributed to manuscript revision.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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