Evolving Concepts in the Treatment of Stage IV Gastric Cancer

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Gastric cancer is the fifth most frequent cancer and the third leading cause of cancer death worldwide. Most gastric cancer patients are advanced at diagnosis and nearly half of resected patients have a recurrence [1]. Their outcome is poor with a median survival not exceeding 10–16 months and the only effective treatment is systemic therapy. In this chapter we discuss the available data on the systemic treatment of advanced gastric cancer and how they could be used in clinical practice.

20.1 The Evolving Role of Systemic Treatment

In the 80s it was clearly shown that combination chemotherapy can prolong survival and improve quality of life but, unfortunately, in spite of the availability of always more active cytotoxic drugs, median survival has plateaued at 9–11 months [2]. This is why an "old" regimen such as the platinum/fluoropyrimidine doublet continues to be the preferred backbone of first-line treatment. Since it has been shown that oxaliplatin and capecitabine can safely replace cisplatin and 5-FU, FOLFOX or XELOX are the most commonly used worldwide [3]. A valuable first-line alternative in patients intolerant to platinum analogs can be FOLFIRI (5-FU, folinic acid, irinotecan), which is effective and well tolerated [4]. The role of a third cytotoxic (docetaxel or epirubicin) added to doublet chemotherapy has been investigated and debated for years. Indeed, both docetaxel and epirubicin-containing triplets yield higher response rates but with more severe toxicities [1].

Similarly to other gastrointestinal tumors, targeted therapies were investigated in the treatment of gastric cancer. However, apart from HER-2 positive tumors, representing no more than 10–15% of gastric cancers, where trastuzumab improved the outcome of patients, no other agents were found effective [5].

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In recent years, immunotherapy with immune checkpoint inhibitors has revolutionized the treatment of many cancers. One of the most relevant immune checkpoints is programmed death-1 (PD-1), a negative costimulatory receptor expressed mainly on activated T cells. Its overexpression has been observed in gastric cancer, making PD-1 pathway inhibition a therapeutic target. The first trial including gastric cancer was the KEYNOTE-012 study. The following phase 2 study, KEYNOTE-059, assessed the safety and efficacy of pembrolizumab in gastric cancer. Based on its results, the FDA granted approval for pembrolizumab in advanced gastric cancer expressing PD-L1 and progressing on or after two or more systemic therapies. However, in the phase 3 trial KEYNOTE-061, pembrolizumab did not demonstrate a significant improvement in survival compared to paclitaxel in second-line therapy. Although these conflicting results make it difficult to define the role of immunotherapy in clinical practice, retrospective analyses showed that pembrolizumab and nivolumab are highly effective in microsatellite instability and Epstein-Barr virus (EBV) tumors, suggesting a role in these specific subgroups of patients. The attempts to move pembrolizumab and nivolumab to first-line treatment produced controversial results. In the KEYNOTE-062 trial, pembrolizumab proved to be noninferior in survival compared with chemotherapy. However, patients receiving chemotherapy had a better survival in the first 6 months of treatment, thus questioning the role of pembrolizumab in patients with more aggressive disease. Furthermore, improved survival was observed only in tumors with PD-L1 combined positive score > 10. This could allow one to select patients, but it was based on a retrospective analysis and the threshold was fixed without any relationship with biology. More recently, in the CHECK-MATE 649 trial, nivolumab in combination with chemotherapy (FOLFOX, CAPOX) resulted in a better survival (13.8 vs. 11.6 months). Similarly to pembrolizumab, it was effective in patients with a combined positive score > 5. Once again, this threshold is not related to biologic findings. Apart from patients with microsatellite instability-high (MSI-H) or EBV tumors, we should wait for further data to define the role of immunotherapy in gastric cancer patients [6].

20.2 From One Line to the Opportunity of Multiple Lines of Treatment

After a 20-year debate, the systemic treatment of gastric cancer moved from the role of first line to that of a second-line therapy. This was due to the disappointing results of trials in first-line chemotherapy as well as to the evidence of a progressive improvement in survival observed in patients receiving sequential lines of treatment. The proportion of patients who remain fit to receive further lines has grown from 20% to 51% for second-line therapy and from slightly above 0 to 25% for the third-line. Understanding of the nutritional issues in advanced gastric cancer patients

and the proactive interventions including nutritional counseling and early supportive care have resulted in better and safer delivery of second- and third-line therapies. At least three drugs, docetaxel, irinotecan and paclitaxel, improved survival in comparison with best supportive care. The strength of these data, in spite of the small sample sizes of the single trials, was that all achieved similar results in terms of efficacy and toxicity. Nevertheless, it was ramucirumab to change mostly the oncologists' attitude toward the management of advanced gastric cancer patients refractory to first-line chemotherapy. Ramucirumab, a monoclonal antibody inhibiting VEGFR-2, was effective in monotherapy (REGARD trial) or in combination with paclitaxel (RAINBOW trial). In monotherapy it achieved the same progression-free survival and survival as those observed in the trials with chemotherapy, with a more favorable toxicity profile. In combination with paclitaxel, ramucirumab obtained an impressive median survival of 9.3 months. It is worth recalling that this value is similar to that obtained in first-line therapy. Based on these data, ramucirumab in combination with paclitaxel is the standard of care for patients with a disease progression after a first line therapy not including taxanes. In patients previously receving taxanes, ramucirumab monotherapy may be effective and safe, sparing toxicity in comparison with chemotherapy [7]. The administration of later lines of therapy is clinically challenging because gastric cancer progresses rapidly in a short time. Physicians may miss the right time for switching to a subsequent therapy without careful follow-up visits. In order not to lose patients, we should remember that although progressive disease may be shown by radiological imaging, more often, the general conditions, clinical symptoms and tumor markers are the most important things to assess in order to switch therapy as early as possible. This is not relevant only for the step from the first to the second line but also from the second to the third line of treatment [7]. In fact, later line treatment has been embraced in both real world and trial settings. Some clinical experiences suggested that a third-line therapy may contribute to an improvement in survival. However, it was the TAGS trial that validated this strategy. This randomized phase III study compared the efficacy and safety of oral cytotoxic trifluridine/tipiracil chemotherapy with placebo in metastatic gastric cancer patients who had received at least two previous chemotherapy lines [8]. It significantly improved survival compared with placebo as well as time to deterioration of the Eastern Cooperative Oncology Group (ECOG) performance status score to 2 or higher. Moreover, it was safe with manageable neutropenia as the most frequent adverse event, making this drug an opportunity in this patient population with a great unmet medical need [9].

A relevant issue is the selection of a patient candidate to later lines. Probably, the factors able to predict a lack of benefit from a second-line therapy are performance status ≥ 2, time to progression on the first line less than 6 months and peritoneal metastasis. More recently, malnutrition has attracted the attention of oncologists [10, 11]. Malnutrition is present in up to 80% of patients and, furthermore, it has been associated with an increased risk of developing treatment-related toxicities [12].

20.3 How to Further Improve the Outcome of Advanced Gastric Cancer Patients

It is undeniable that the improvement of outcome of advanced gastric cancer patients depends on the availability of effective drugs. Nevertheless, we should not forget that our skill in the management of patients in first line influences the clinical history of most patients in later lines. At least three different points may help us to design specific treatment strategies in order to offer the best approach for each patient. Advanced disease is not a homogenous disease. It includes two different situations: a locally advanced unresectable disease and metastatic disease. The prognosis is different. In locally advanced disease, median survival goes beyond 12 months, while it is only 6 months or less in metastatic disease. Also, the aim of treatment is different. In locally advanced unresectable disease we should pursue tumor shrinkage in order to make an unresectable disease resectable. This means that highly active regimens should be preferred. A three-drug regimen, like FLOT, may be a reasonable option. On the contrary, in the metastatic setting the aim of treatment is to improve survival and quality of life and, therefore, the treatment strategy is based on different lines of treatment. In reality, even the term "metastatic disease" does not define a homogeneous group of patients as it may include patients with oligometastatic disease or multiorgan metastatic disease. The definition of oligometastatic disease is still debated [13, 14]. Probably we should include within this term all the patients with a radically resectable metastatic disease. Nevertheless, these patients should not undergo upfront surgery but only after a response to or long-lasting stable disease on systemic treatment. Once again, the question is which is the best regimen. In a retrospective analysis, the FLOT regimen seems to be an appropriate option even if we have to wait for the prospective randomized trial.

Another crucial aspect is how long to continue treatment. In the case of a clinical response or stable disease, can we discontinue therapy waiting for a progression before restarting treatment? It is not clear. Chemotherapy prolongation until disease progression is the standard of care on the basis of published international guidelines and randomized phase III clinical trials. Nevertheless, this strategy is consistently associated with cumulative toxicity and prompt development of drug resistance, with disease progression after 4–6 cycles. The cumulative toxicity rate with continued administration of chemotherapy could also negatively affect the patients' quality of life. This reinforces the need to extend the time to progression in the subgroup of patients with a responsive disease. A reasonable strategy could be deintensification, withdrawing cisplatin or oxaliplatin. Probably we should individualize the approach, carefully assessing patients in treatment vacation in order to do not miss performance status deterioration. It is undeniable that patients have achieved an improvement in survival over recent years and that this has been mainly due to a better treatment strategy. New treatments are urgently needed, but the greatest challenge will be to understand which cancer subgroup deserves a specific therapy and to design clinical trials tailored on these subgroups, in order to transfer the molecular classification acquisitions into clinical practice and to minimize the number of patients who receive a systemic treatment without any molecular selection.

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