

Insights across the continuum of care for patients with advanced gastric cancer

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Advanced gastric cancer: 2015 state of the art of a still incurable disease

Gastric cancer (GC) is among the most important health problems in oncology, with 25,000 new cases expected in the US in 2015 (1), a yearly global incidence approaching one million new cases (2) and representing one of the most relevant causes of cancer-caused deaths worldwide. Despite notable improvements in the knowledge of its complex underpinning disease biology (3), significant advances in the systemic therapy and the introduction of targeted agents in the clinical practice, the prognosis of patients with advanced disease remains unacceptably poor, with a dismal median survival of less than 12 months (4).

In general, palliative chemotherapy consisting of a combination regimen has become the universal standard of care for patients with advanced gastric cancers because of its efficacy in prolonging survival and improving the quality of life (5). Around 40% of patients display tumors expressing potentially druggable targets (6); only HER2, however, has been recognized as valuable in the clinical practice so far (7). Fit patients with HER-2 negative tumors are optimal candidates for combination regimens including a fluoropyrimidine, cisplatin, with or without a third drug (typically an anthracycline or docetaxel), as well as irinotecan-containing regimens (8). In case of HER-2 overexpression or amplification, trastuzumab could be added to a standard fluoropyrimidine and cisplatin-based regimen on the basis of the ToGA trial results (9). Other interesting molecules, such as MET-inhibitors, are currently being studied in prospective randomized trials.

After disease progression, a considerable proportion of patients may be offered a second-line treatment, but this proportion significantly differs between European and Asian studies, ranging from 15% to over 60% (10). Recent local reports have shown that approximately 50% of patients receive a second-line systemic treatment (11). In this setting, several randomized trials have confirmed that the use of single-agent chemotherapy (12-14), that of an antiangiogenic alone such as ramucirumab (15, 16) or apatinib (17), or the combination of the VEGFR2 inhibitor and a taxane (18) have all enlarged the median survival of these patients. In general, the decision to opt for supportive care alone rather than chemotherapy relies on patients' performance status as well as on other prognostic factors (19, 20). In the second-line setting, Catalano et al. found five factors independently associated with poor overall survival: declined PS (PS of 2 or lower), low hemoglobin levels ($\leq 11,5$ g/l), presence of ≥ 3 metastatic sites of disease, time to progression under first-line therapy ≤ 6 months, and CEA level > 50 ng/ml. In the absence of data deriving from prospective randomized trials, these clinical factors may help to select patients who may derive benefit from second-line therapy (21).

Timing of palliative and supportive care in the advanced cancer phases

Unfortunately, metastatic GC patients may be sometimes unfit for standard medical treatments and are exclusively candidate for supportive care. While the decision to offer supportive care alone or chemo-

therapy depends on the patient's medical conditions, there is emerging evidence that early incorporation of care principles may significantly improve patients' outcomes and reduce distress and aggressive measures at the end of life (22, 23). Consequently, the prompt integration of palliative care in the treatment trajectory is suggested whenever the treatment line is considered as a continuum (24). In this landscape, an accurate plan deserves to be re-discussed at each significant time-point (25), bearing in mind that multiple issues affecting physical, psychic and social aspects, as well as spiritual and practical activities, may cause suffering for the patients, their families, and their caregivers along the disease course.

Firstly appeared more than 30 years ago, the definition of palliative care has markedly changed over time. Nowadays, its meaning is multifaceted and many concepts lie beneath these words (26). Briefly, palliative care may currently be considered a holistic field of study and a ground of action that aims at addressing the needs of patients with advanced, incurable cancers and those of their family or caregivers. In the last few years, multiple studies have demonstrated the benefit of palliative care in terms of quality of life, symptom improvement, prognostic understanding, patients' satisfaction, emotional burden, appropriate health service use, and possibly survival. As a result, all major scientific societies interested in this topic, including ASCO, ESMO and AIOM, have spurred the integration of palliative care in the treatment of cancer patients (27-29). As said before, the sooner the palliative care is introduced, the better may be the results (30). In fact, not only three unblinded randomized trials have demonstrated that timely interventions may ameliorate symptom control, produce a higher treatment adherence and improve the quality of life of patients presenting with advanced disease (31-33), but also the early adoption of a palliative program may decrease useless in-hospital admissions during the late stage of the disease (34). In this regard, the use of the term "palliative care" has been replaced by "supportive care", which may be conducive to earlier referrals and help to address the patients' need for unplanned presentations, especially if the consultations take place in an outpatient clinic (35). As a whole country, Italy has a strong tradition of palliative care, with a total of 27

centers awarded and actively acting toward improving cancer patients' supportive care. Moreover, our country has a strong commitment in palliative and simultaneous care, and a national commission is hardly working on this topic (36). Importantly, along with the widespread awareness that early initiation of supportive care improves patients' physical and spiritual well-being, comes the need of innovative healthcare models and appropriately reshaped outpatient services, with the engagement of policy makers and all possible stakeholders.

The paradigmatic example of nutritional problems in gastric cancer patients

Entering into more disease-specific details, palliative interventions addressed to patients with advanced or metastatic GC are aimed at relieving different disease-related conditions such as nutritional disturbances (which possibly have a mechanic or organic cause), bleeding, pain, and may result in life prolongation as well as in improved quality of life. For the purpose of this manuscript, we will further focus on the nutritional aspects of advanced GC patients, which may be considered as a paradigmatic example that requires a multidisciplinary approach throughout the entire disease course.

Since the early beginning, GC patients are frequently affected by malnutrition, anorexia and weight loss: the symptom burden may affect their prognosis, and increase the length of hospital stay, healthcare costs, reducing the quality of life, and survival. Nutritional support is highly recommended both in the pre- and in the postoperative period. Indeed, GC patients are at high risk for malnutrition during the whole disease course. Although a number of causes may play a role in impairing the nutritional status of the GC patients, a misbalance between energy expenditure and nutritional supplementation is the central physiologic derangement leading to cancer-induced weight loss. Many different scores have been proposed to assess the baseline patients' nutritional status (37), which may be easily used in the clinical practice. Among these scores, Onodera's Prognostic Nutritional Index (38), the systemic inflammation-based Glasgow Prognostic Score (39),

the Nutritional Risk Indicator (40), and the Cancer Cachexia Study Group (41) represent useful tools for an initial evaluation and should be part of a routine evaluation of patients to provide a timely nutritional support.

Patients with advanced disease frequently present with weight loss, clinical signs of lipolysis, muscle wasting, anorexia, chronic nausea, inflammation, and asthenia. In particular, the cancer anorexia-cachexia syndrome is a frequent paraneoplastic condition occurring in half of all oncologic patients and it is considered as a poor prognosticator. Impaired nutritional state during cancer treatment has also been associated with more treatment interruptions and compromised treatment efficacy; consequently maintaining adequate energy intake during therapy is mandatory and nutritional counseling is very important (42).

Gastric cancer patients in whom surgical treatment is not deemed a valuable option may be particularly challenging: in those subjects physiological nutritional support is often limited by obstruction from the on site primary tumor; in selected cases enteral feeding can be proposed after potential candidates are screened appropriately to identify what causes are potentially affecting their intake; a careful risk-benefit analysis should be performed to justify use of parenteral nutrition, because of potential complications. Moreover, self-expandable metallic stents may be placed to counteract malignant gastric outlet obstruction regardless of patients' age, as suggested by recent endoscopic and surgical case series.

Conclusions

The delivery of high-quality supportive and palliative care is crucial in patients diagnosed with advanced gastric carcinoma, and requires cooperation and coordination among healthcare professionals (including medical and radiation oncologists, surgeons, experts on rehabilitation, pain medicine, anesthesiology, and palliative medicine), as well as nurses, social workers, and psychologists (44). In the "continuum of care project" for advanced cancer patients, early provision of supportive care provides evident benefits (45), and collaborative efforts to improve its adoption are warranted.

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