EUR. J. ONCOL., vol. 19, Suppl n. 1, pp. 24-25, 2014

Gastric Cancer: therapeutic choices in advanced disease

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Gastric cancer remains one of the leading causes of cancer mortality worldwide even thought its incidence has been decreasing in recent years. Radical surgical resection still represents the only potentially curative treatment. Unfortunately, more than half of gastric carcinomas are diagnosed in an advanced stage, when resection is no longer possible. In this setting chemotherapy is still the main treatment option for patients with advanced disease. Median overall survival (OS) of 8-12 months has been reported in patients undergoing chemotherapy compared with 3-5 months for those treated with best supportive care alone (1). Drugs such as fluorouracil (5-FU), cisplatin, docetaxel, and, less commonly, paclitaxel, epirubicin, and irinotecan are major components of conventional regimens. Oxaliplatin, capecitabine, S-1, and mytomicin C are also being used for the treatment of gastric cancer. Combination chemotherapy has been shown to be associated with a statistically significant (p=0.001) survival benefit compared to monotherapy in a meta-analysis of several clinical trials (2). This corresponded to a small but clinically relevant 1-month mean average survival benefit. This meta-analysis also showed that including anthracyclines in a 5-FU-cisplatin combination had a modest survival advantage over cisplatin-5-FU alone (HR 0.77). Finally, the meta-analysis also showed that three-drug combinations had a significant survival benefit compared to two-drug combinations. Several clinical trials (3-6) investigating first-line therapy in advanced gastric cancer suggested that a triplet chemotherapy regimen might have a survival benefit over doublets but the evidence is not fully convincing since these results are mostly dependent on older studies. Adding more chemotherapeutic agents seems to confer more benefit but at the same time inevitably adds toxicity, thus to date, a triplet chemotherapy combinations is not an established global standard as yet. Besides, in the daily clinical practice, administering a three-drugs treatment may prove difficult in advanced gastric cancer patients, who often present with multiple co-morbidities and poor performance status. Moreover clinical trials demonstrating a potential benefit in adding a third drug to a doublet regimen are relatively old and most of the patients included did not receive a second-line treatment. Consequently in this scenario a doublet with a fluoropyrimidine and platinum is still an acceptable alternative and remains the cornerstone of gastric cancer treatment. On this basis, the definition of the standard chemotherapy regimen for advanced gastric cancer remains a matter debate.

Although different histological subtypes of GC have been identified, in the daily clinical practice and for the purpose of medical management, GC is usually considered as a single disease. Recently, epidemiological, pathological and clinical data have been incorporated to define a new classification of GC that identifies three tumor subtypes: type 1, proximal non-diffuse GC, with the bulk of the tumor (>80%) located in the gastric cardia and characterized by a non-diffuse pattern of infiltration; type 2, diffuse GC, located anywhere in the stomach with an entirely diffuse pattern of infiltration; type 3, distal non-diffuse GC, with the bulk of the tumor located in the distal or mid

stomach and a dominant pattern of intestinal type carcinoma (7). Furthermore, Shah et al have demonstrated that these GC subtypes, classified on the basis of histology and anatomic location, have also distinct gene expression profiles, supporting the hypothesis that GC subtypes may be distinguished molecularly (8).

One of the clinical implications of this heterogeneity in GC biology is the possible different sensitivity to chemotherapy treatment among the different GC subtypes. Differences in response to treatment between different subtypes have been reported by a subset analysis of the FLAGS trial, which showed better overall for patients with diffuse GC when treated with cisplatin/S-1 compared to cisplatin/5-FU (9). Genetic and translational studies are warranted to improve the understanding of molecular drivers and pathways of different GC subtype that may help to identify prognostic and predictive biomarkers as well as to identify specific targets for therapy.

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