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ORIGINAL ARTICLE

Systemic Therapy for Advanced Gastric Cancer

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ABSTRACT

Gastric cancer is the fourth commonest cancer worldwide, with nearly a million new patients being diagnosed with this disease per year, of whom 55% are in East Asia. Regrettably, despite the availability of potentially curative resection, between 50 and 90% of these patients die as a result of disease relapse. This article discusses systemic therapy for advanced gastric cancer, with a focus on cytotoxic chemotherapy and targeted therapy for unresectable, metastatic or recurrent disease. Older-generation cytotoxics entailed 5-fluorouracil, the platinum compound cisplatin, and anthracyclines (doxorubicin and epirubicin). In this disease setting, clinical trials have addressed the role of palliative chemotherapy versus best supportive care, as well as single agent versus combination chemotherapy. New cytotoxic agents that have been tested include oral fluoropyrimidines (capecitabine and S-1), other platinum derivatives (oxaliplatin), taxanes (docetaxel and paclitaxel) and irinotecan. Outcomes associated with various treatment regimens incorporating these newer agents and old-generation combination chemotherapy have been compared. The main biological agents that have been tested include those that act on 3 classes of molecular targets, namely human epidermal growth factor receptor 2, vascular endothelial growth factor, and epidermal growth factor receptor.

Key Words: *Antineoplastic combined chemotherapy protocols; Neoplasm metastasis; Neoplasm recurrence, local; Stomach neoplasms; Treatment outcome*

中文摘要

進展期胃癌的全身性治療

楊明明

胃癌位居世界最常見癌症的第四位，每年都有接近一百萬名新診斷的胃癌病人，其中有55%在東亞地區發生。可惜的是，縱使有可為胃癌作根治性的切除術，仍然有五至九成的病人因胃癌復發而死亡。本文探討晚期胃癌的全身性治療，並集中討論對不能切除、轉移性或復發性胃癌的化療及標靶治療。上一代的化療藥物有5-氟脲嘧啶、順鉑（鉑類合成藥物）及蒽環類抗癌藥物（阿霉素及表阿霉素）。在這些病例中，許多臨床研究都嘗試比較緩解化療和最佳支持治療，以及比較單藥化療和聯合化療。經測試的新一代化療藥物包括口服氟尿嘧啶類藥物（卡培他濱及S1），其他鉑類藥物（奧沙利鉑），紫杉醇類藥物（多烯紫杉醇及紫杉醇）及伊立替康。並比較了由多種上一代藥物與新一代藥物聯合化療進行的各種治療方案的效果。經測試的主要生物製劑包括了用於應對三種分子標靶，它們分別為人類表皮生長因子受體-2、血管內皮生長因子、以及表皮生長因子受體。

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INTRODUCTION

Despite a decreasing incidence of gastric cancer worldwide, this disease remains a leading cause of cancer mortality.[1] Although early-stage disease can be treated by curative resection, a significant proportion of patients present with locally advanced or metastatic disease. Even in the western world, at diagnosis more than 80% of patients have an advanced gastric cancer and a poor prognosis. The management of advanced disease has made significant progress since the 1990s, with a parallel change in clinical practice.

CHEMOTHERAPY VERSUS BEST SUPPORTIVE CARE

In selected, fit patients with advanced gastric cancer, randomised studies have demonstrated that systemic chemotherapy offers moderate but clinically significant advantages in terms of increased survival (about 6 months), symptom control, and quality of life. Such benefits are evident when compared with patients having best supportive care only, in whom median survival is reported to be in the range of 3 to 5 months only.[2-4]

The 'older' generations of cytotoxic agents that have been tested in gastric cancer were mainly 5-fluorouracil (5-FU), cisplatin, and the anthracyclines. Other agents that have been evaluated include leucovorin, etoposide, methotrexate, and mitomycin C. Trials that compared single agent of 5-FU with combinations of 5-FU and cisplatin have shown a survival trend in favour of combination therapy.[5,6]

In the UK, 2 large randomised trials conducted with a view to evaluating combination chemotherapy using the now well-known combination of epirubicin/5-FU/cisplatin (ECF) showed that this type of regimen conferred superior efficacy and quality of life.[7,8]

A meta-analysis by Wagner et al[9] assessing the role of combination versus single-agent chemotherapy reported that the former was associated with a statistically significant survival benefit in patients with metastatic gastric cancer. Other data suggest that the addition of an anthracycline to cisplatin-based regimens also improves survival.[9]

Over the past decade, clinical research in systemic palliative therapy has focused on the oral pyrimidines capecitabine and S-1, the platinum compound oxaliplatin, the taxane docetaxel, the topoisomerase I inhibitor irinotecan as well as molecular targeted therapies.

NEWER GENERATIONS OF COMBINATION REGIMENS

Oxaliplatin and capecitabine in combination with epirubicin were compared to a conventional combination regimen of ECF in the UK REAL 2 study.[10] Capecitabine is an oral, inactive 5-FU prodrug. It is extensively absorbed by the gut mucosa and its final conversion to 5-FU in tumour cells is facilitated by a higher expression of the enzyme thymidine phosphorylase than in normal tissues. This non-inferiority, randomised phase III trial indicates that oxaliplatin may replace cisplatin and that capecitabine may replace 5-FU in the ECF regimen without any significant difference in response rate or survival.[10]

In the ML17032 study, capecitabine/cisplatin and 5-FU/cisplatin were compared as first-line treatments for advanced gastric cancer and the capecitabine/cisplatin combination showed noninferiority for progression-free survival versus 5-FU/cisplatin in the first-line treatment of advanced gastric cancer.[11]

The other new-generation oral pyrimidine S-1 has been studied in combination with cisplatin and was shown to confer outcomes similar to cisplatin and 5-FU (ASCO 2009[12]). In the SPIRITS study, this combination revealed a trend towards better survival than S-1 alone.[13]

Yet another agent in the treatment of gastric cancer is the topoisomerase I inhibitor irinotecan. The efficacy of irinotecan in gastric cancer has been demonstrated in several phase II studies, both as monotherapy and in combination regimens. Results from phase III trials that compared combination of irinotecan/5-FU/leucovorin to 5-FU/cisplatin or 5-FU/leucovorin with or without a third agent showed a trend towards better survival for the former regimen.[14-16] However, a meta-analysis has not shown a definitive benefit of irinotecan-containing regimens in comparison to other combinations.[9] In a more recent study reported by Boku et al,[17] S-1 was shown to be non-inferior to 5-FU, whilst irinotecan/cisplatin was shown to be non-superior.

Docetaxel is the taxane that has been evaluated in a randomised phase III setting in combination with 5-FU and cisplatin in the V325-study.[18] In this trial involving over 450 patients, the triplet regimen with the addition of docetaxel was found to be significantly superior to the doublet combination; in patients with advanced

gastric cancer it yielded an improved response rate, time to progression, overall survival, and quality of life.[18] However, reported treatment-related toxicities (episodes of neutropenia, neutropenic fever, and diarrhoea) were more frequent and a cause for concern.

With the introduction of novel drug administration schedules and the emergence of new chemotherapeutic agents, modern systemic chemotherapy for advanced gastric cancers can achieve 30 to 60% objective response rates. However, overall survival remains consistently around 9 to 11 months, and for some regimens, this is achieved at the expense of significant treatment-related toxicities.[19]

INCORPORATION OF MOLECULAR TARGETED THERAPY

Novel drugs including epidermal growth factor receptor–targeted therapies, matrix metalloproteinase inhibitors, and inhibitors of angiogenesis are presently being tested in patients with advanced gastric cancer.

The recently reported ToGA study[20] is one of the first phase III studies that assessed the therapeutic efficacy of trastuzumab (the monoclonal antibody against human epidermal growth factor receptor 2 [HER2]), in combination with capecitabine / cisplatin.[20] A total of 594 patients were randomly assigned to trastuzumab plus the chemotherapy regimen versus the chemotherapy alone, and yielded a median overall survival of 13.8 months in the former group, compared to 11.1 months in those assigned to chemotherapy alone (hazard ratio = 0.74; p = 0.0046). These encouraging results establish the role of anti-HER2 therapy for HER2-positive advanced gastric or gastroesophageal junction cancer.

Bevacizumab, a monoclonal antibody that binds specifically to the vascular endothelial growth factor, has also been studied in combination with capecitabine / cisplatin in a randomised phase III setting in the AVAGAST study.[21] This showed a significant improvement in progression-free survival from 5.3 to 6.7 months in the bevacizumab-containing arm of the study, which did not translate into a statistically significant improvement in overall survival (10.1 vs 12.1 months, p = 0.1002).

CONCLUSION

Presently, there are a number of acceptable chemotherapy regimens that can be recommended for the palliative therapy of gastric cancer in addition to best supportive care. A careful evaluation of the patient status and the toxicity profiles of the different regimens should be performed before starting therapy. Based on a global perspective, the mainstay of cytotoxic treatment mainly involves a doublet containing a platinum compound in combination with a fluoropyrimidine. Should a triplet be considered, the addition of epirubicin or docetaxel appears acceptable. For novel biological therapies to demonstrate a clinically significant effect, their biological rationale has to be tested in appropriately selected patients who might stand to benefit. At present, in patients with HER2-positive gastric cancers, the molecular targeted agent trastuzumab can be considered. The presently available data do not support the routine use of other targeted therapies in gastric cancer, but several ongoing studies with novel agents should prove helpful in deciding whether to incorporate them into the therapeutic armamentarium directed at this disease.

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