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Geographic differences in approach to advanced gastric cancer: Is there a standard approach?

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Abstract

Gastric cancer is one of the leading causes of cancer related deaths worldwide. Regional differences in gastric cancer are evident between Asian and Western societies with respect to etiology, prevalence, clinicopathologic features as well as treatment pattern of the disease. For patients with advanced gastric cancer (AGC), chemotherapy has been found to improve survival and quality of life compared to best supportive care alone. But contrast to other tumors such as colon or pancreatic cancer, there are regional differences in outcome in gastric cancer. Various geographic/ethnic, biology and treatment strategies may contribute to these differences. In the first line setting, cisplatin and fluoropyrimidine based therapies remain the backbone of treatment for advanced gastric cancer in Asian and Western patients, although there is preference for S1 in Asia and 5FU in the West. A third agent may be added in patients with good performance status. Recent trials from Asia and Europe demonstrate an advantage for second line chemotherapy. Irinotecan and taxanes are the most commonly used agents. The introduction of

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trastuzumab into the frontline therapy of AGC has ushered the age of targeted therapy and personalized medicine in this disease. In this article, we will review the various first and second line chemotherapy regimens in AGC, taking into account regional differences including potential biomarkers.

Keywords: Advanced gastric cancer; Chemotherapy; Regional differences; Biomarkers

1. Introduction

Gastric cancer remains the second leading cause of cancer death worldwide [1]. Approximately 1 million new cases are diagnosed with 800,000 deaths attributed to this disease annually [1]. Except for Korea and Japan, where surveillance programs are widely practiced, approximately two thirds of gastric cancer patients will present at an advanced stage. Even after curative intent surgical resection, loco-regional and distant relapse is a common problem. In the advanced setting, palliative chemotherapy remains the mainstay of treatment. Patients receiving chemotherapy live longer than those on best supportive care (BSC) alone with an increase in median survival of approximately 6 months based on a meta-analysis [2].

There is no consensus on the approach and management of advanced gastric cancer (AGC) as it varies from region to region. Survival outcome differs between Asian and Western populations in gastric cancer; this may be due to several factors including differences in biology, stage migration, and treatment pattern.

Various combinations of platinum and fluoropyrimidines are commonly used for first line treatment of AGC. In many Asian countries, chemotherapy doublets are frequently used, while in Western countries, triplet regimens are more widely adopted. Nonetheless, median survival time even with contemporary regimens is typically less than one year [3–5].

Second line therapy for AGC is more commonly practiced in East Asia than in Western countries. Until recently, there was no standard of care chemotherapy in patients who progressed on platinum and 5FU based therapies. Emerging data from Korea shows that single agent chemotherapy (irinotecan or docetaxel) improved overall survival compared to BSC [6].

In this article, we will attempt to review and explore the different regional approaches to AGC, discussing first and second line chemotherapy regimens incorporating predictive biomarkers. Discussion of molecular targeted agents is beyond the scope of this paper.

2. Difference in outcomes: Asia vs West

Various discrepancies exist in the outcomes of early gastric cancer between Asian and Western countries. These may be attributed to differences in the location of the primary tumor (distal vs proximal), histology (intestinal vs diffuse), diet and early diagnosis as well as the management of the disease [7].

In early stage gastric cancer, the outcome of surgery alone has been superior in Asia, especially in Japan, compared to Western countries [8,9]. Western patients have higher incidences of diffuse histology and more proximal tumors which is associated with a worse prognosis [10–12]. On the other hand, treatment of early stage gastric cancer in Japan has focused on extended lymph node dissection (D2 resection) in comparison to Western countries where less extensive lymph node dissection is performed. Whether the improved outcome is due to more extensive D2 resection or a difference in biology or simply stage migration associated with more lymph node sampling is a controversial question [13].

Earlier randomized Dutch trial did not show improve outcome in western population who underwent D2 resection [14]. However 15-year follow-up showed that D2 lymphadenectomy was associated with lower loco regional recurrence and gastric-cancer-related death rates than D1 surgery [15].

Group from Memorial Sloan Kettering Cancer Center (MSKCC) attempted to compare surgical outcomes of gastric cancer patients at MSKCC to those in Japan and Korea with two retrospective reviews. This is a reasonable comparison as D2 resection is routinely performed at MSKCC, similarly to Japan and Korea. The first study, published 10 years ago, showed that favorable outcomes for gastric carcinoma patients in Japan were primarily explained by differences in tumor location, a greater frequency of early stage disease, and more accurate staging. However, the study showed similar 5-year survival rates when stratified by tumor location and T-stage [10].

However the second study comparing gastric cancer patients from MSKCC to those in Korea came to different conclusion. In this study, Korean patients demonstrated better outcomes compared to MSKCC patients even when matched by T stage and location [12]. As was the case for Japanese patients, there were more patients with lower node positivity and early stage disease in the Korean population. When multivariate analysis with a validated gastric cancer nomogram was used, disease specific survival (DSS) for Korean gastric cancer patients was significantly more favorable than that of MSKCC patients by 20–30%, suggesting inherent biological differences. In this study, patients who received neo-adjuvant treatment were excluded to decrease the influence of treatment on outcome of US patients. Another potential explanation may have to do with lymph node dissection. About 73% of Korean patients had more than 30 lymph nodes removed compared to 29% of MSKCC patients suggesting an impact of the pattern of practice. Other factors