MINI REVIEW - THE PRESENT STATE OF THE CHEMOTHERAPY FOR ADVANCED GASTRIC CANCER

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Abstract

A large number of trials have been done to improve the survival of the patients with advanced gastric cancer, but no chemotherapeutic regimen is superior to 5FU alone in the term of the survival. 5FU alone or FP has still been a referent regimen in gastric cancer. However, newly promising agents have been appearing, and several trials have been starting. These trials should be continued to break through the limitation of the survival in patients with advanced gastric cancer.

Introduction

Gastric cancer continues to be one of the most common malignancies in Japan. The development of diagnostic modalities and surgical techniques has improved the...
prognosis, but associated mortality is still the second highest next to lung cancer (Cancer Statistics in Japan'01). This is due to the lack of an effective treatment for unresectable advanced or recurrent gastric cancer, and it is very important to develop an effective chemotherapy.

A number of agents are active in gastric cancer, and some randomized trials demonstrated chemotherapy that a 5-fluorouracil (5FU)-based regimen provides superior survival in patients with advanced gastric cancer, being compared with the best supporting care (Murad, Santiago et al., 1993, Glimelius, Hoffmann et al., 1994, Pyrhonen, Kuitunen et al., 1995). However, this survival benefit appears to be limited, and no combination treatment is recognized as the standard for gastric cancer and it has been continued to explore the more effective combination chemotherapy for advanced gastric cancer.

In this review, we look over the clinical trials that have been undergone to improve the clinical benefit for unresectable advanced or recurrent gastric cancer, and introduce our trial using new drugs for gastric cancer, docetaxel (Taxotere; TXT) and irinotecan hydrochloride (CPT-11).

**Phase II trials**

A number of combination chemotherapy has been developed and clinical phase II trials have been done.

The first combination chemotherapy was FAM, consisting of 5FU, doxorubicin (ADR) and mitomycin C (MMC). In late 1970th, Macdonald reported that the response rate (RR) and the median survival time (MST) after FAM treatment were 42% and 9.0 months (Macdonald, Schein et al., 1980), and this regimen was thought to be the standard therapy in 1980. But the subsequent studies revealed that cumulative RR and MST were 30% and 6 to 9 months (Preusser, Achterrath et al., 1988), and FAM is not thought to be the standard therapy. In Japan, a randomized phase II study comparing tegafur plus MMC with UFTM, consisting of tegafur and uracil (UFT) plus MMC, was carried out, and the study demonstrated that UFTM was a higher RR of 23.5% than tegafur plus
MMC but no survival differences were observed between two arms (Kurihara, Izumi et al., 1991).

The impacts on the treatment of gastric cancer in 1980th to 1990th, were the development of cisplatin (CDDP) and etoposide (ETP), and the introduction of the biochemical modulation. Moertel et al. proposed FAP treatment, consisting of 5FU, ADR and CDDP, and reported that RR and MST were 50% and 9 months (Moertel, Rubin et al., 1986). But Collinan et al. conducted the control trial comparing FAP treatment with 5FU alone and concluded that FAP was not superior in terms of the survival and worse in side effects (Cullinan, Moertel et al., 1994).

Preusser et al. proposed EAP treatment, consisting of ETP, ADR and CDDP, and reported that RR and MST were 64%, involving a complete remission (CR) of 21%, and 9.0 months (Preusser, Wilkeet et al., 1989). EAP treatment was paid attention to, and Lerner et al. tried this treatment and reported that RR and MST were 33%, involving a CR of 8%, and 7.5 months, but treatment-related deaths of 11% had occurred (Lerner, Gonin et al., 1992). The Japanese trial also showed a high RR and favorable MST but approximately treatment-related deaths of 10% (Shimada, Yoshida et al., 1991), and now EAP is not accepted due to the strong side effects.

The regimen based on the biochemical modulation involves FP, ECF, ELF, PELF and FAMTX. FP consists of 5FU and CDDP, and these two drugs modulate each other biochemically. Lacave et al. reported that RR and MST after FP treatment were 41% and 10.6 months (Lacave, Baron et al., 1991), and Ohtsu et al. reported that they were 43% and 7 months in the Japanese clinical oncology group (JCOG) trial (Ohtsu, Shimada et al., 1994). 5'-deoxy-5-fluorouridine (5'DFUR) is an orally masked compound of 5FU, and the combination of CDDP and 5'DFUR, as a substitute of 5FU, was tried in Japan, and the result of the phase II was that RR and MST were 50% and 8.9 months, respectively (Koizumi, Kurihara et al., 1993). ECF treatment consists of 5FU, CDDP and epi-doxorubicine (EPI), and Findlay et al. reported that RR and MST were 71%, involving a CR of 12%, and 8 months, respectively (Findlay, Cunningham et al., 1994).
ELF treatment consists of ETP, 5FU and leucovorin (LV), which modulates 5FU biochemically. This regimen was developed for the elder patients, and Wilke et al. reported that RR and MST were 53%, involving a CR of 12%, and 11 months, respectively (Wilke, Preusser et al., 1990). PELF treatment consists of CDDP, 5FU, LV and EPI, and the mechanism of the biochemical modulation works among CDDP, LV and 5FU, and Cocconi et al. reported that RR and MST were 43% and 8 months, respectively (Cocconi, Bella et al., 1994). FAMTX treatment is the combination of sequential methotrexate (MTX) and 5FU, combined with ADR or EPI, and LV for the rescue of sequential MTX and 5FU. An European organization for research on treatment of cancer (EORTG) gastrointestinal group study showed that RR and MST were 33% and 6 months, respectively (Wils, Bleiberg et al., 1986). In Japan, only sequential MTX and 5FU rescued by LV has been used, and the multi-institutional phase II study of this combination showed that RR and MST were 40.5% and 7.6 months, respectively (Murakami, Ota et al., 1987).

The impacts in late 1990th were the development of the granulocyte stimulating factor (GCS-F) and the introduction of the dose intensive chemotherapy. Weekly PELF treatment is the dose intensive regimen that PELF is administrated weekly using GCS-F. Cascinu et al. reported that RR and MST after weekly PELF treatment were 62%, involving a CR of 17%, and 11 months, respectively (Cascinu, Labianca et al., 1997). PE-HDLF consists of high dose 5FU and LV, CDDP and EPI, and Chen et al. reported that RR and MST were 72.5%, involving a CR of 22.5%, and 9 months (Cheng, Yeh et al., 1998).

**Phase III trials**

There have been several reports of randomized phase III studies in patients with unresectable advanced or recurrent gastric cancer.

In Korea, Kim et al. conducted a phase III randomized study of FP vs. FAM vs. 5FU alone, and reported that FP provided a significantly higher RR but no superiority in MST as compared with FAM or 5FU alone (Kim, Park et al., 1993). Cullinan et al.
conducted a North Central Cancer Treatment Group trial that compared three-drug regimens with 5FU alone, and showed no significant survival advantage in three drug-regimens (Cullinan, Moertel et al., 1994). In Europe, Wils et al. conducted an EORTC phase III trial of FAMTX vs. FAM, and reported that FAMTX demonstrated significant superior RR and MST than FAM (Wils, Klein et al., 1991). The subsequent EORTC phase III study, however, did not prove any superiority of FAMTX over FP or ELF (Vanhoefer, Rougier et al., 2000). Another randomized phase III study from the United Kingdom compared FAMTX with ECF, and demonstrated that RR and MST in ECF are superior to those in FAMTX (Webb, Cunningham et al., 1997). In Japan, a JCOG phase III study of FP vs. UFTM vs. 5FU alone was carried out, and Ohtsu et al. reported that FP demonstrated a higher response rate but no survival advantage as compared with 5FU alone (Ohtsu, Shimada et al., 2003).

On all of the phase III studies, no regimen is superior to 5FU alone in terms of the survival. The limitation of the MST is less than 10 months and the reference regimen has still been 5FU alone or FP in the treatment of advanced gastric cancer.

New drugs and new regimens

New drugs such as irinotecan hydrochloride (CPT-11), docetaxel (TXT), paclitaxel (TXL) and S-1 (1 M tegafur – 0.4 M gimestat – 1 M otastat potassium) have been developed and promising in the treatment of advanced gastric cancer. CPT-11 acts by inhibiting DNA topoisomerase I, and the RR in a single agent phase II study was 23.3% (Futatsuki, Wakui et al., 1994). TXT and TXL are semisynthetic taxoids, and work antimitotic agents, enhancing microtubule assembly and inhibiting depolymerization of tubulin. TXT showed 17.1% of the RR in the single agent phase II study (Taguchi, Sakata et al., 1998, Mai, Sakata et al., 1999), and TXL showed a RR of 28% and a MST of 234 days in the single agent phase II study (Yamaguchi, Tada et al., 2002). S-1 is an orally masked compound of 5FU and showed a RR of 49% and a MST of 250 days in the single agent phase II study (Sakata, Ohtsu et al., 1998).
CPT was initially combined with CDDP, and this combination regimen showed a RR of 49% and a MST of 322 days (Boku, Ohtsu et al., 1999). This regimen and S-1 have been thought to be candidates for the standard regimen, and JCOG has been undergoing a randomized phase III study of CPT and CDDP vs. S-1 vs. 5FU alone in Japan.

On the other hand, several new combinations of new and conventional drugs have been being designed and tried. We also designed a biweekly administration regimen of TXT combined with CPT-11 for 4 weeks as one cycle (Yoshioka, Sakata et al., in press). The rationale of this combination is that the drugs have different action mechanisms and safety profiles. For chemotherapy in patients with gastric cancer, 5FU derivatives and 5FU-based regimens are generally used. Our combination does not include 5FU nor its masked compounds, and in spite of the very small study population this combination showed a high response rate in patients with previous chemotherapy that involved 5FU or its masked compound in our dose escalation study of this combination regimen. Our combination of TXT and CPT-11 may potentially be used in patients who failed to respond to regimens including 5FU.

References


