30

Multimodal Therapies for Upper Gastrointestinal Cancers – Past, Now, and Future

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1. Introduction

Gastric and esophageal cancers are one of the most aggressive malignancies worldwide. Complete surgical resection offers the only chance of cure but many cases are presented at advanced stages or recur even after R0 resections. In gastric cancer (GC), 5-year survival rates (SRs) of stages II and III after curative resection range respectively from 30%-49% and 10-20% in Western countries, and respectively 70-80% and 40-50% in Japan and Korea (Fujii et al., 1999; Hundahl et al., 2000; J.P.Kim et al., 1998; Shimada et al., 1999). With regard to esophageal cancer (EC), the 5-year SRs in older series were 14-20% in the United States (Daly et al., 1996; Ries et al., 2007) and ranging from 3 to 11% in European countries, with an average of 10% (Faivre et al., 1998) while they improved to 42% in a recent series (Rice et al., 2009; Ruol A et al., 2009), which is comparable to those (36-46%) after an esophagectomy in Japan (The Japan Esophageal Society). Even in Japan, however, T3 or stage III EC, the most frequently encountered tumor depth or tumor stage, has exhibited respectively lower 5-year SRs of 27-29% and 17-20% after esophagectomy (Ando et al., 2000; The Japan Esophageal Society). Although stage-specific survival rates differ between reports from Western and Asian institutions, the survival decline according to the stage progression suggests that recurrence does occur even for those who undergo curative resection. Furthermore, a more extended (>D2) lymph node dissection (LND) in GC unfortunately fails to improve survival outcomes (Sasako et al., 2008).

Such disappointing treatment results in GC and EC even in Japan -where aggressive LND has been performed- have reminded researchers a plateau effectiveness of, and little likelihood of further improvement by, surgical therapy only. These facts have encouraged physicians to establish more effective multimodal strategies to improve survival, including newly developed regimens incorporating molecular targeting agents as well as to determine candidate molecules or genes that could help establish individualized therapies. These multimodal therapies have mainly consisted of chemotherapy (CTx), radiotherapy (RTx), and chemoradiotherapy (CRTx) administered after curative resection (adjuvant settings), or for recurrent or inoperable diseases (advanced settings), or before surgical resection (neoadjuvant settings). Recently, CRTx has become a focus of research, because of the radiosensitizing properties of some chemotherapeutic agents that could potentiate the anticancer activities of both CTx and RTx (Kleinberg et al., 2007).

Table lists the theoretical advantages and disadvantages of adjuvant and neoadjuvant treatments (Rice et al., 2003). Adjuvant and neoadjuvant treatments require balancing advantages and disadvantages to maximize treatment effects. This chapter focuses on past, current, and potential future directions in the field of multimodal therapies in GC and EC.

	Advantages	Disadvantages
Adjuvant treatment	Prevention of potential recurrence from occult micrometastasis which would become overt postoperatively.	Inability to assess final treatment effects until diseases recur.
	Less consideration for increase in morbidity and mortality that would be sometimes harm in case of neoadjuvant treatment.	Destruction of vasculature that decreases delivery of drugs or oxygen compromising CTx and/or RTx effects.
	Treatment decision based on the full staging information, which can avoid unnecessary treatment in patients who may not otherwise require it, i.e., in patients with earlier stage of the disease than expected.	Preclusion of early commencement of therapy if patient recovery delays due to postoperative complications or reduced functional status. Requirement of longer period to recover from surgery allows tumor cells for further growth.
	Especially in EC, relief of tumor-associated complaints such as dysphagia or alimentary support by surgically-placed feeding tube, allowing for better tolerance of postoperative therapy.	In RTx, removal of target that make definition of radiation field more difficult.
Neoadjuvant treatment	Increased surgical R0 resection rate by downstaging which would otherwise have been regarded as incurable (R1/R2 resection).	Surgical delay due to toxicities that would cancel the potential survival benefit of responders.
	Early elimination of undetectable micrometastasis.	Loss of opportunity to undergo surgery by tumor growth during treatment period in nonresponders.
	Intact vasculature that maintains accessibility of drugs to the tumor bed and oxygenation, realizing more effective CTx and/or RTx.	No reliable methods available to predict tumor response that could discriminate responders and non-responders before treatment.
	Determination of tumor and patient specific chemo(radio)sensitivity that would be applicable to postoperative treatment.	Increased surgical complaints due to preoperative treatment-related toxicities.
	Possibility to administer a more intensive regimen because of the maintained physical and nutritional state. The same regimen would become more toxic if given postoperatively due to surgical-related complication.	Preclusion of effective regimen due to dysphagia or tumor related worse nutritional state, especially in EC.
		Possibility of overtreatment for early stage tumor because treatment is based on clinical stage that is not necessarily accurate.

Table 1. Advantages and disadvantages of adjuvant and neoadjuvant treatment [Rice TW, et al. 2003].

2. General considerations

In consideration of the establishment of multimodal therapies against GC and EC, one should bear in mind the difference in surgical treatment and pathology between Japan and the West. First, the scope of LND influences local tumor control rate and postoperative survival. A wider scope of LND has the theoretical potential to reduce local recurrence rates, which may improve postoperative survival. Second, it is also a fact that a wider scope of LND increases postoperative morbidity and mortality, which may cancel the anticipated survival benefit of LND. This phenomenon is especially observed in the West, providing one reason for the difference in the standard scope of LND between here and Japan. As a result, for GC, the standard scope of LND is a D2 (second-tier node dissection) in Japan but a D1 (first-tier node dissection) in the West, and for EC, the routinely performed node clearance encompasses three fields (cervical, thoracic, and abdominal) or at least any two of the three fields in Japan, while it encompasses a limited area in the West. Since the effect of hospital volume on a perioperative mortality hazard is larger than those on hazards for death at 5 years postoperatively (Bilimoria et al., 2008; Birkmeyer et al., 2002), the perioperative patient control reflects the subsequent overall survival; thus, LND by specialists is now an important issue. Third, a wider scope of LND results in a more accurate nodal staging than a narrower one. Therefore, under conditions of a limited extent of LND, judgement regarding R0 resection is not always accurate, and resections deemed R0 might sometimes be actually equivalent to R1 resection. For example, in a Dutch trial, 38% of GC patients classified as stage II on D1 dissection were reclassified as stage IIIA on D2 dissection (Bunt,1995). This discordance is reflected by the stage migration phenomenon which implies that a narrower scope of LND results in a significant risk of understaging. Therefore, results of clinical trials of multimodal therapies are undoubtedly influenced if they recruit such understaged patients. Fourth, the scope of LND depends on the pathological characteristics of the tumor. With regard to EC, adenocarcinoma is observed at a substantial ratio (43-56%) in the United States (Daly et al., 1996; Trivers et al., 2008), while squamous cell cancer comprises a majority in Japan (The Japan Esophageal Society), the incidences twice those of the United States (90% vs. 38%) (Trivers et al., 2008). Such histological differences reflect tumor location and surgical approach. In Japan, the incidences of middle and lower third thoracic EC were respectively 50% and 25% (The Japan Esophageal Society), whereas those in the United States were respectively 25% and 50% (Daly et al., 1996). Considering that upper thoracic or cervical nodal involvement occurs more frequently in the middle third than lower third thoracic EC, such histological and topographical differences also influence surgical approach and ultimately the scope of LND. In Japan, a right thoracotomy is a main approach while a transhiatal approach is considered in the West (Hulscher et al., 2001). Finally, the different stances in surgical therapy between Japan and the West reflect the different stances of multimodal therapies. Since a wider scope of LND is more effective in local tumor control than a limited one, CTx rather than CRTx has been developed in Japan for the purpose of preventing systemic relapse rather than local recurrence, whereas CRTx rather than CTx has been developed in the West for the purpose of preventing both local and systemic relapse.

3. Gastric cancer

3.1 Adjuvant setting

Many randomized controlled trials (RCTs) have been conducted to assess the advantage of adjuvant CTx on survival compared with surgery alone. However, they have shown mixed

results and have been mostly disappointing. The difficulties in making definitive conclusions concerning the significance of adjuvant CTx are accounted for -at least in part- by the small size of the studies and suboptimal CTx regimens. Many trials recruited relatively small numbers of patients -usually less than 200- and were therefore inadequate to detect clinically significant survival differences between the CTx arm and surgery alone arm. In addition, many CTx regimens employed old types of drug with low response rates (RRs) and short durations of response. Therefore, the negative results of most previous clinical trials do not necessarily mean that the adjuvant CTx does not work.

Several meta-analyses of adjuvant trials have been published (Earle & Maroun, 1999; GASTRIC Group, 2010; Hermans et al., 1993; Hu et al., 2002; Janunger et al., 2002; Liu et al., 2008; Mari et al., 2000; Oba et al., 2006; Panzini et al., 2002; Zhao & Fang, 2008) in order to overcome the drawbacks of small patient accrual and to assess any potential benefit by adjuvant therapy that may have been missed in the individual trials. Unfortunately, definitive evidence concerning benefits of adjuvant CTx is lacking, with results ranging from an odds ratio for death of 0.56-0.9 to no benefit. However, the first meta-analysis (Hermans et al., 1993), which failed to demonstrate a clear benefit of adjuvant CTx, was later updated by an inclusion of 318 patients who had been erroneously omitted from the initial analysis, resulting in a reduction of the odds ratio for death to a significant 0.82 (Hermans & Bonenkamp, 1994).

Nevertheless, criticism still persists as to the methodologies applied in these meta-analyses that make this interpretation too complicated. For example, there was a great heterogeneity among individual studies in terms of quality of surgery, adjuvant therapy regimens administered, clinical stage, and intervals between surgery and the commencement of CTx. Accordingly, patient recruitment was not uniform within each meta-analysis. Some meta-analyses included studies of palliative resections and curative resections, or studies of CTx, RTx, and immunotherapy together. The quality of surgery could not be evaluated because the scope of LND was not always clarified. Studies with old generation drug(s) and those with newer generation drug(s) were also included together. In addition, one meta-analysis (Hu et al., 2002) included a previous meta-analysis (Hermans et al., 1993).

The most recent meta-analysis (GASTRIC Group, 2010), which was the first patient-level analysis, was published in the year 2010. It demonstrated both mortality and relapse hazard reduction by 18% each by adjuvant CTx. This trend was also reproduced irrespective of the number of CTx drugs (monochemotherapy and polychemotherapies). Furthermore, a survival improvement of 6% by CTx at 5 years postoperatively was maintained during the ensuing 5 years. These consecutive results of the meta-analyses suggest that the benefit of adjuvant CTx change from 'none or inconclusive or borderline' to 'significant'.

Subset metaanalysis have demonstrated inconsistent results, however. When Asian and non-Asian adjuvant trials were grouped together or analyzed separately, survival benefits were seen only in the non-Asian studies (Earle & Maroun, 1999), or only in the Asian studies (Janunger et al., 2002), or in both (Zhao & Fang, 2008). The extant metaanalyses are therefore difficult to interpret due to significant heterogeneity. Interestingly, in the pivotal Japanese RCT for adjuvant CTx (JCOG9206-1) (Nashimoto et al., 2003), the total recurrence rate at 69 months was almost double in the surgery only arm than in the CTx arm (13.8% vs. 7.1%), indicating a possible role by CTx for the prevention of recurrence. Against these backgrounds, several large RCTs of postoperative or perioperative CTx have been conducted in Japan, the United States, and Europe, and each result has been recently published.

The ACTS-GC (Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer) trial is so far the largest adjuvant RCT conducted in Japan, in which oral S-1, a new generation of fluoropyrimidine derivative, was administered for 1 year as an adjuvant treatment (Sakuramoto et al., 2007). The survival benefit of S-1 at three years postoperatively has also been confirmed at 5 years (Sasako et al., 2010). The results are consistent with the previous metaanalysis demonstrating the survival advantage of oral fluoropyrimidine containing adjuvant regimen (Oba et al., 2006). Of note in this trial is that most of the recruited patients underwent D2 or a wider scope of LND, and even under such circumstances of qualified surgery, the oral fluoropyrimidine derivative alone was able to render benefits in an adjuvant setting. However, caution is required when these results are applied to clinical use. The subanalysis of the ACTS-GC trial revealed that survival benefit was maintained in stages II and IIIA GC but disappeared in stage IIIB. Such stage specific survival differences suggest that oral fluoropyrimidine alone lacks power to exhibit statistically meaningful survival advantages in more advanced stages.

The phase III intergroup-0116 trial (INT0116) is one of the most important adjuvant trials against adenocarcinoma of the stomach or esophagogastric junction ever conducted in North America (Macdonald et al., 2001). The adjuvant treatment in this study was a CRTx consisting of fluorouracil, leucovorin, and extra-beam radiation delivered to the tumor bed with 2cm beyond the proximal and distal margins of resection as well as to the areas of regional draining lymph nodes. Adjuvant CRTx yielded a significant prolongation of disease free survival (DFS) and overall survival (OS) at 3 years postoperatively (Macdonald et al., 2001). More than six years of median follow-up confirmed no deterioration of survival over time (Macdonald et al., 2004), making this regimen optimal as the standard of care in the United States. However, there has also been some criticism directed towards this study.

First, the extent of surgery performed in this study has been a focus of much debate. The trial has been criticized for the surgical undertreatment of patients: 54% and 36% of the patients in the trial respectively underwent a D0 and a D1 LND despite a recommendation of a D2 LND in the trial protocol. Such noncompliance clearly undermined survival and led to a high relapse rate of 64% in the surgery only arm after a median follow-up of 5 years, the results contrasting sharply with those of the JCOG9206-1 trial (Nashimoto et al., 2003). Considering that more than two thirds and 85% of the recruited patients respectively had T3/T4 diseases and were node positive, the survival benefit by CRTx seen in this study seemed to be simply a compensation for the control residual disease left by the inadequately limited surgery (D0 or D1), which could otherwise be resected by a D2 LND. Second, usage of 5FU as a radiosensitizer and chemotherapy of 5FU and leucovorin seemed appropriate at the time when INT-0116 was designed (in the 1980's) and executed (in the 1990's); however, new generation agents with a superior antitumor activity and greater radiosensitizing effect continue to be developed (Rice et al., 2003).

As discussed in the General Considerations section, this context raises another important insight that outcomes of adjuvant therapy undoubtedly depend on the quality of surgery, in particular, on the scope of LND. The incidence of locoregional recurrence after curative resection has been higher in the West (Roviello et al., 2003) (45%) than in Japan (Maehara et al., 2000) (22%), suggesting a benefit from the routine performance of a D2 LND for local tumor control. Such a benefit is guaranteed by the safe performance of a D2 LND in Japan, with a 0-2.2% mortality rate (Fujii et al., 1999; Maruyama et al., 1987; Maruyama et al., 2006; Nashimoto et al., 2003; Sano et al., 2002). Indeed, in the JCOG9206-1 trial, 98% of the patients

underwent a D2 or greater LND, with just one (0.8%) postoperative death in the surgery only arm. The number of patients with local recurrence was two (1.6%) in the surgery only arm and none in the adjuvant treatment arm, suggesting a remarkable local control rate by the Japanese style D2 LND. Therefore, convinced of the benefit of a D2 LND, Japanese investigators have always been reluctant to conduct any trial comparing D2 with D1 LND. In contrast, operative mortality remains high within Europe, ranging between 5-16% (Lepage et al., 2010). Under these circumstances, the initial phase III trials conducted in the West demonstrated that a D2 LND provided neither survival improvements nor decreased relapse rates, and that it was even harmful in terms of a 43-46% morbidity and 10-13% mortality (Bonenkamp et al., 1995; Bonenkamp et al., 1999; Cuschieri et al., 1996; Cuschieri A et al., 1999; Hartgrink et al., 2004a; Songun et al., 2010). Such higher D2-associated morbidity and mortality were initially considered to nullify its potential survival benefit by local control; however, a subsequent long-term 15-year follow up of a Dutch trial observed significantly higher local recurrence rates and cancer-related death rates in D1 than in D2 (Songun et al., 2010), leading the authors to conclude that a D2 LND has efficacy for local control and can be recommended for resectable GC, given that a safer, spleen-preserving D2 LND is available. Subsequent studies have supported this procedure-related safety. Several nonrandomized trials have also demonstrated no differences in morbidity and mortality between a D1 and a D2 or wider LND (Bösing et al., 2000; Edwards et al., 2004; Danielson et al., 2007; Zilberstein et al., 2004). The RCTs conducted in the dedicated centers in the West elucidated a safer performance with a D2 or wider LND, with morbidity and hospital mortality being 17-22% and <2%, respectively, if resection of the pancreas and/or spleen was performed for selected patients.

Considering that postoperative CRTx can be a substitution for a D2 LND, adjuvant CRTx constitutes an alternative option for countries where a D1 LND is the primary treatment or at institutions where surgeons are not keen on a D2, whereas its effect is questionable where a D2 dissection is both routine and safe -such as in Japan or in some Western specialized centers (Degiuli et al., 2004a; Degiuli et al., 2004b; Degiuli et al., 2010; Kulig et al., 2007; Sano et al., 2004; C.W.Wu et al., 2004; C.W.Wu et al., 2006). Interestingly, a Korean group (S.Kim et al., 2005) reported the superiority of adjuvant CRTx over surgery alone in gastric cancer patients undergoing a D2 dissection. Since the CRTx protocol in this study was identical to that of INT0116, the results, although observational, suggest that CRTx is promising even for patients undergoing a qualified LND.

Two RCTs assessing the benefits of perioperative chemotherapy have been conducted. The MAGIC trial (Medical Research Council Adjuvant Gastric Infusional Chemotherapy) (Cunningham et al., 2006) was a randomized perioperative CTx trial in United Kingdom for patients with stage II or higher resectable adenocarcinoma of the stomach, esophagogastric junction, or lower esophagus. In this trial, the perioperative CTx consisted of three preoperative and three postoperative cycles of epirubicin, cisplatin, and fluorouracil (ECF). The perioperative CTx significantly improved 5-year DFS and 5-year OS. Another was a French trial (FNCLCC94012-FFCD9703) comparing perioperative cisplatin and 5FU (CF). Again, however, there are several limitations and criticisms regarding these trials. The scope of LND in MAGIC trial was not standardized, with a D1 or a D2 LND being left to the discretion of the surgeons, resulting in only 41% of the patients undergoing a D2 LND. Curative resection rates in the surgery only arm accounted only for 66% (MAGIC trial) or 73% (FFCD trial) of the patients, suggesting that both were not purely adjuvant CTx trials

and likely recruited extremely advanced cases. Perioperative CTx may be harsh because of the relatively higher rate (9%) of not completing the three planned cycles of ECF, and of low rates of commencement (55%) and completion (42%) of the postoperative ECF, predominantly due to toxic effects, early disease progression, patient request, and postoperative complications. In addition, the 30-day mortality rate in both arms of the MAGIC trial was approximately 6%, which is relatively higher than those of a D2 (0-5%) (Degiuli et al., 2004a; Degiuli et al., 2004b; Degiuli et al., 2010; Kulig et al., 2007; Nashimoto et al., 2003; Sano et al., 2004; C.W.Wu et al., 2004; C.W.Wu et al., 2006) or wider scope of LND (0.8-2%) (Kulig et al., 2007; Sano et al., 2004) in Japanese and Western specialized institutions. Pathological T1 disease patients comprised 8% of the surgery only arm, suggesting that preoperative staging was not necessarily accurate and such earlier stage patients received unnecessary CTx, which would be more harmful than beneficial. Finally, the continuous infusion of 5FU that requires an infusion pump and long term infusional access may be associated with a risk of catheter-related complications.

Taking these results concerning benefit and harm of LND into account, a D2 surgery is at least equal to an adjuvant CRTx with D0/D1 surgery, and an adjuvant S-1 improve survivals more than a D2 LND alone -at least in Japan. Encouraged by the positive results of INT0116 and MAGIC trials, a more combined multidisciplinary approach has been investigated in a CRITICS trial, in which adjuvant CRTx (investigational arm) after 3 preoperative cycles of ECC (epirubicine, cisplatin, capecitabine) and D1 surgery (clearance of >15 nodes) was compared with 3 adjuvant cycles of ECC (control arm) after the same preoperative ECC and the same quality of surgery (http://www.critics.nl).

3.2 Advanced setting

Evidence of benefits of CTx for patients with advanced or recurrent GC was obtained from the previous RCTs demonstrating a significantly improved survival by CTx as compared with the best supportive care (Glimelius et al., 1994; Murad et al., 1993; Pyrhönen et al., 1995). In Western countries, FAMTX (5FU, adriamycin, methotrexate) then became the standard regimen from the results of the EORTC randomized study, demonstrating the superiority of FAMTX over FAM (5FU, adriamycin, mitomycin C) with regard to median survival time (MST) (42 weeks vs. 29 weeks), RR (41% vs. 9%), and toxicity (Wils et al., 1991). Subsequently, a standard FAMTX regimen was compared with ECF. The RR and MST by ECF (46% and 8.7 months) were both found to be superior to FAMTX (21% and 6.1 months) (Waters et al., 1999). In addition, ECF was less toxic, afforded patients better quality of life, and was more favorable in cost effectiveness as compared with FAMTX (Webb et al., 1997), leading the investigators to propose an ECF regimen as a standard therapy. A recent systematic review revealed that the best survival results are achieved with a three-drug regimen containing 5FU, anthracycline, and cisplatin (Wagner et al., 2006).

In this century, docetaxel, one of the new generation agents, has become available and been recognized as a promising agent, being incorporated in several clinical trials. The non-overlapping toxicity profiles of docetaxel, cisplatin, and 5FU (DCF), as well as synergism among these agents in vitro (Maeda et al., 2004) in a schedule dependent manner or in human GC xenografts (Kodera et al., 2005), warrant this combination to be evaluated in treating GC. In Europe, a three-arm, randomized phase II study was conducted to compare DCF (docetaxel, cisplatin, 5FU), DC (docetaxel, cisplatin), and a standard reference regimen ECF (Roth et al., 2007). The RR and MST of the DCF (37% and 10.4 months) were superior to

those of the DC (18% and 11.0 months) and ECF (25% and 8.3 months), leading to the recommendation of DCF as an investigational regimen for further clinical trials. Similarly, in the United States, a randomized phase II trial found that DCF and DC were both active while DCF produced higher RR (43%) than DC (26%) (Ajani et al., 2005b). The DCF was then further positioned as an investigational regimen in a subsequent phase III trial (Van Cutsem et al., 2006), in which DCF was found to be significantly superior to CF with regard to RR (37% vs. 25%, p=0.01) and MST (9.2 months vs. 8.6 months, p=0.02). In addition, DCF was able to maintain patient performance status longer. However, a higher incidence of grade 3/4 hematological toxicities (82% of neutropenia, 65% of leucopenia, and 29% of neutropenic fever) emphasized a need for a vigilant patient selection and careful patient management and monitoring, which might preclude its more widespread acceptance as a new treatment option.

The requirement for a balance between survival gains and experienced toxicities has prompted several modifications of the DCF regimen to improve tolerability. A weekly administration of DCF may yield an improved safety profile without compromising the efficacy. In lung, breast, and prostate cancers, toxicities were less with weekly taxane than with triweekly taxane, while OS did not significantly differ between the two schedules or was even better in weekly taxane (Bria et al., 2006; Engels & Verweij, 2005; Sparano et al., 2008). There are several trials of DCF modifications (C.P. Li, 2010; Lorenzen et al., 2007; Overman et al., 2010; Park et al., 2005; Sato et al., 2010; Tebbutt et al., 2010). Among these investigations, GASTRO-TAX-1 (Lorenzen et al., 2007) proved modified DCF to have a remarkably prolonged MST (17.9 months) and median time to progression (TTP) (9.4 months), with a reduced incidence of grade 3/4 neutropenia (22%) and febrile neutropenia (5%).

On the other hand, in Japan, JCOG conducted a randomized study comparing mitomycin C (MMC) plus tegafur with MMC plus UFT (uracil and tegafur) (UFT-M). Although MSTs were equivalent in both arms (6 months), significantly higher RR (25%) in the UFT-M arm than in the MMC plus tegafur arm (8%) (Kurihara et al., 1991) led the investigators to recommend UFT-M as a candidate regimen for further clinical trials. JCOG then conducted a three-arm RCT comparing UFT-M, CF, and a continuous infusion of 5FU (JCOG9205) (Ohtsu et al., 2003). In this trial, patient recruitment for the UFT-M arm was stopped due to poor survivals with significant toxicities, and the survival curves of the remaining two arms were overlapping. Taking efficacy and toxicity together into account, a continuous infusion of 5FU monotherapy with a MST of 7.1 months remained as a reference arm for further clinical trials.

At the end of the last century, when S-1 became available, JCOG conducted another three-arm RCT comparing the continuous infusion of 5FU monotherapy (reference regimen) with S-1, or irinotecan plus cisplatin (JCOG9912) (Boku et al., 2009). The investigators observed a noninferiority of S-1 to 5FU, and the convenience of oral administration lead to the conclusion that a continuous infusion of 5FU monotherapy could be replaced by S-1 for the first-line CTx.

Encouraged by these results, several randomized trials have been conducted by placing S-1 as a reference arm, and some trials have recently yielded results (Y.H. Kim et al., 2011; Koizumi et al., 2008; Narahara et al., 2011). Taking all these into account, a S-1 plus cisplatin combination (CS) is currently considered as a standard regimen in Japan for the treatment of advanced GC.

Globally, this combination has been investigated in a FLAGS study (First Line Advanced Gastric Cancer Study) (Ajani et al., 2010), in which 1053 patients were randomly assigned to either receive infusional CF or CS in non-Asian patients. Unfortunately, CS failed to prolong MST (8.6 months) as compared with CF (7.9 months). However, significant safety advantages of CS over CF suggested the possibility of the substitution of S-1 for infusional 5FU. The different results between the Japanese SPIRITS trial and Caucasian FLAGS trial are ascribed to the different recommended doses of S-1 between the two studies, presumably due to different metabolic profiles among races. Tegafur, a cytotoxic component of S-1, is converted to 5FU by cytochrome P450 2A6 (CYP2A6). Racial differences for gene polymorphism of CYP2A6 have been identified (Yoshida et al., 2003) (Daigo et al., 2002; M. Nakajima et al., 2006), and the variants are more frequent in Asians than in Caucasians (M. Nakajima et al., 2006). Since such polymorphism accounts for a lower enzymatic activity, Caucasians have a relatively higher enzymatic activity than Asians, leading to a faster conversion from FT to 5FU, more accumulation of 5FU, and consequently less tolerance to S-1. Accordingly, the recommended dose of S-1 in the FLAGS study (50mg/m2/day) was lower than that (80mg/m2/day) for Japanese (Ajani et al., 2005a). Another reason for the different results of the two trials may be the different ratio of patients receiving second-line therapies, which were respectively 74% and 75% in the CS and S-1 arms in the SPIRITS trial (Koizumi W et al., 2008), while they were respectively 30% and 33% in the CS and CF arms in the FLAGS trial (Ajani et al., 2010).

In China, a similar randomized study is now ongoing. In this study, the S-1 dose is the same (80mg/m2/day, twice daily) as that in Japan, but cisplatin is given in four administrations, each being 20mg/m2 (http://www.ClinicalTrial.gov. NCT 01198392).

Although the results of the FLAGS trial were unfortunately negative, an oral administration route is undoubtedly convenient; its advantages include the alleviation of the requirement for control of a central venous catheter implantation, which in turn may improve the patient's quality of life. Against these backgrounds, there have been attempts to replace intravenous chemotherapy agents with the oral chemotherapy. Two-by-two designed RCTs (REAL-2 trial) have evaluated whether capecitabine (oral fluoropyrimidine) could be an alternative to infusional 5FU (Cunningham et al., 2008) and also whether cisplatin could be replaced by the new platinum compound oxaliplatin. In the REAL-2 study, the incorporated agents were epirubicin (E), cisplatin (C), 5FU (F), capecitabine (X), and oxaliplatin (O). Some 1002 patients were randomly assigned to receive either one of triplet therapies such as ECF, EOF, ECX, and EOX. Interestingly, MST by EOX (11.2 months) was longer than that (9.9 months) of a current European standard regimen ECF. Toxicities of capecitabine and 5FU were similar. Cisplatin requires hydration while oxaliplatin does not. As compared with cisplatin, oxaliplatin was associated with lower incidences of grade 3/4 neutropenia, alopecia, renal toxicity, and thromboembolism, but with higher incidences of grade 3/4 diarrhea and neuropathy. These results, together with the results of the recent RCTs (Al-Batran et al., 2008; Y.K. Kang et al., 2009), suggest the feasibility of substituting 5FU with capecitabine, or cisplatin with oxaliplatin. Indeed, the superiority of capecitabine over 5FU has been confirmed by a recent meta-analysis (Okines et al., 2009)

Trends towards oral administration have prompted researchers to investigate whether 5FU can be replaced by oral fluoropyrimidine S-1 in the DCF regimen. Surprisingly, a combination of docetaxel, cisplatin, and S-1 (DCS) yielded remarkable RR (84%) and MST (23 months) (Sato et al., 2010). The optimal doses of docetaxel and/or cisplatin of this triplet therapy have been investigated in several phase I studies (Fushida et al., 2009; Hironaka et

al., 2010; Nakayama et al., 2008). No requirement of hydration in oxaliplatin has prompted the substitution of cisplatin with oxaliplatin in the DCS regimen, forming a new triplet docetaxel, oxaliplatin, and S-1. However, it achieved modest MST (12 months) with 38% grade 3/4 neutropenia, despite high RR and CR rates (60% and 7.5%) (Zang et al., 2010). Since these studies are preliminary, the efficacy and safety of DCS should be confirmed by large-scale clinical trials. Finally, a multicenter phase II trial has very recently demonstrated that an S-1 and oxaliplatin combination (SOX) can be a substitution for a CS regimen; this has just been indicated as a standard regimen in Japan or a safer regimen than FP in the West. The SOX regimen yielded remarkable MST (16.5 months), while grade 3/4 neutropenia developed in 22% of the patients (Yamada et al., 2010).

Another important concern lies in the fact that the net survival time cannot necessarily be achieved by a single regimen. As discussed earlier, negative results of the FLAGS trial may be attributable to the relatively small number of patients receiving second-line therapies. One should bear in mind that most of the chemotherapy regimens introduced above could yield a median TTP of less than 7 months, suggesting the urgent need for the establishment of effective second-line regimens. The contribution of a second line treatment on survival has been also confirmed by the combined analysis of two large Japanese randomized trials (JCOG9205 and JCOG9912) (Takashima et al., 2010). Because the number of active drugs against GC is increasing, attempts to establish the best second or third line regimen(s) are important, as has been seen for colorectal cancer as well. Currently, several RCTs have been conducted or are now ongoing to provide one answer for this unresolved issue.

3.3 Neoadjuvant setting

Many RCTs for neoadjuvant CTx (NAC) trials have been performed, but the majority have failed to provide evidence concerning the superiority of NAC as compared with controls (Hartgrink et al., 2004b; Imano et al., 2010; Nio et al., 2004; Schuhmacher et al., 2010; Yonemura et al., 1993; C.W. Zhang et al., 2004). The negative results may be accounted for by the small number of recruited patients -usually less than 200, heterogeneous tumor stage- i.e., some studies recruited earlier T1/T2 tumors, heterogeneity in the scope of the LND or drug administration route, and allowance of additional postoperative adjuvant therapies. Therefore, the NAC value remains controversial because of a lack of well-powered trials, and the results of several meta-analyses are conflicting (H. Li et al., 2010; W. Li et al., 2010; A.W. Wu et al., 2007). Although the most recent two analyses revealed benefits of NAC in terms of OS, resection rate, and tumor down staging without increasing perioperative mortality (H. Li et al., 2010; W. Li et al., 2010), the effect of NAC alone on OS remains questionable since individual pure NAC trials, i.e., comparison between surgery alone and NAC without postoperative CTx, failed to demonstrate positive effects on survival (W. Li et al., 2010). Similarly, surgery plus postoperative CTx with or without NAC provided similar survival results (Nio et al., 2004).

As discussed in the General Considerations section, the selection of patients who receive the most benefit from NAC is an important concern (Table). The benefit of NAC was observed only in more advanced (T3/T4) cancers but not in earlier (T1/T2) cancers (W. Li et al., 2010), suggesting that any potential survival benefit may be confined to those patients at greatest risk of relapse (T3/T4). Whether early stage GC received the same benefit of NAC remains unclear since serosa-negative gastric cancer in Japan exhibited 83% DFS and 86% OS by a D2 LND without adjuvant CTx (JCOG9206-1) (Nashimoto et al., 2003). Similar favorable

survival results by qualified surgery in earlier stage GC were also reported from the West (Roukos et al., 2001; Siewert et al., 1998), suggesting that patients with a low risk of recurrence can be cured with adequate surgery alone (Roukos, 2004). The benefit of NAC is also influenced by the quality of surgery. As discussed in the MAGIC trial, positive effects of NAC, if present when the combined surgery is a <D2 LND, can be attributable to a mere substitution for a LND rather than the effects of the NAC itself. When determining the NAC regimen, one providing the highest likelihood of tumor shrinkage is theoretically the best regimen for NAC because subsequent surgery can extirpate the residual disease of the NAC. In this sense, several NAC trials using CS, which provides currently the highest RR (74%) (Koizumi et al., 2003), are ongoing in Japan. First, JCOG0501 is a RCT comparing surgery alone with neoadjuvant CS for type 4 or large type 3 GC (http://www.ClinicalTrial.gov. NCT00252161). Second, JCOG0405 is a phase II study investigating the efficacy of neoadjuvant CS for GC with bulky second-tier nodes or positive paraaortic nodes (Kawashima et al., 2008). The third study is a comparison between surgery alone and neoadjuvant CS, both containing adjuvant S-1 for stage III GC (http://www.ClinicalTrial.gov. NCT00182611).

4. Esophageal cancer

4.1 Adjuvant setting

In the West, a number of RCTs have been conducted to investigate the efficacy of adjuvant CTx or adjuvant RTx. A subsequent meta-analysis, however, failed to find any survival benefit at three years by adjuvant CTx or at one year by adjuvant RTx (Malthaner et al., 2004). This conclusion concerning the efficacy of adjuvant CTx was, however, drawn from the pooled data of only 2 studies. So far, there have been no RCTs evaluating adjuvant CRTx versus surgery alone (Malthaner et al., 2004); however, several phase II trials have demonstrated that adjuvant CRTx appeared to prolong survival (Bédard et al., 2001; Rice et al., 2003).

In Japan, an earlier RCT of adjuvant CTx consisting of cisplatin plus vindesine conducted in the 1980s failed to exhibit a survival benefit over surgery alone (JCOG8806) (Ando et al., 1997). JCOG then conducted a RCT (JCOG9204) comparing adjuvant CF with surgery alone (Ando et al., 2003). Although 5-year SR did not differ between the two arms (p=0.13), adjuvant CF was able to yield significantly improved 5-year DFS (p=0.04), which was more evident in node positive patients. In Japan, no adequate RCTs have been conducted to assess adjuvant RTx or adjuvant CRTx as compared with surgery alone.

4.2 Neoadjuvant setting

Multimodal therapies as a neoadjuvant setting have been developed mostly in the West, but their efficacy is conflicting. The significance of survival prolongation by NAC has changed from inconclusive in earlier metaanalyses (mortality hazard=0.88, 95% CI=0.75-1.04) (Malthaner et al., 2004; Malthaner et al., 2006) to just reaching positive (mortality hazard=0.90, 95% CI=0.81-1.00, p=0.05) (Gebski et al., 2007). The significance was more evident in adenocarcinomas by subgroup analyses by histology (mortality hazard=0.78, CI=0.64-0.95, p=0.014) (Gebski et al., 2007). Fortunately, treatment morbidity and mortality did not differ between NAC and surgery alone (Malthaner et al., 2006; Urschel et al., 2002). However, the positive NAC effects on survival (Gebski et al., 2007) seem to be influenced by one MRC study (Medical Research Council Oesophageal Cancer Working Group 2002) with

the largest sample size (n=802), while most of the included RCTs in this meta-analysis in which the number of recruited patients was less than 100 showed no or marginal benefit for NAC. Although the survival benefit of the MRC study has been recently confirmed by a long-term follow-up study (Allum et al., 2009), the interpretation of this study requires caution, because the 5-year SR of the surgery only arm was only 17% despite half of the recruited EC being T3 or less (Medical Research Council Oesophageal Cancer Working Group 2002). This low SR contrasts with that (52%) of the surgery only arm in the JCOG9204 study, in which 65% and 55% of patients had T3/T4 and stage III/IV diseases, respectively. Conceivably, the advantage of neoadjuvant treatment is more likely to be demonstrated when SR in the control (surgery only) arm is lower. In addition, the survival benefit initially observed in adenocarcinoma in the MRC study disappeared in the later analysis (Allum et al., 2009). Finally, although NAC could enhance the chance of R0 resection, the pattern of the first recurrence was similar between the neoadjuvant CTx arm and surgery only arm (Allum et al., 2009), suggesting that NAC showed no clear trend toward fewer patients with distant metastasis as the first site of metastasis. These characteristics were also confirmed in the second largest study (RTOG8911) (Kelsen et al., 1998).

There are several systematic overviews concerning neoadjuvant RTx. These studies have consistently failed to reveal any improvement of survival by neoadjuvant RTx in patients with potentially resectable EC (Arnott et al., 2005; Ask et al., 2003; Malthaner et al., 2004).

In contrast, there are increasing expectations for neoadjuvant CRTx which are also supported by a recent RCT showing that neoadjuvant CRTx resulted in a significantly higher pathological CR rate compared with neoadjuvant CTx (Stahl et al., 2009). This could translate into a marginally significant (p=0.07) improvement in 3-year SR from 28% in neoadjuvant CTx to 47% in neoadjuvant CRTx in patients with locally advanced adenocarcinomas of the esophagogastric junction. Although some inconsistencies do exist (Luu et al., 2008), several neoadjuvant randomized CRTx trials have been conducted in the West and elucidated the rates of downstaging (Fiorica et al., 2004), R0 resection (Urschel & Vasan, 2003), and 3-year survival (Fiorica et al., 2004; Urschel & Vasan, 2003) in favor of neoadjuvant CRTx. Such survival benefits in favor of neoadjuvant CRTx were observed in both adenocarcinoma and squamous cell carcinoma (Gebski et al., 2007).

In Japan, the results of JCOG9204 have led to the subsequent RCT (JCOG9907) to determine which timing of the CTx administration is optimal, preoperatively or postoperatively. Preoperative CF was superior to postoperative CF both in progression free survival (PFS) (p=0.044) and OS (p=0.014), suggesting that neoadjuvant CF is superior to adjuvant CF or surgery alone. Whether the novel active regimen such as DCF or weekly DCF in GC can be extrapolated to EC has been investigated in a phase I/II trial (JCOG0807).

Comparing Japanese trials with Western ones, one should notice the dramatic difference in terms of postoperative mortality and survival outcomes. In Japan, surgery with at least 2-field LND yielded >50% 5-year SR with extremely low mortality, while Western studies demonstrated increased mortality (>5%) with lower 5-year SR. In addition, neoadjuvant CRTx resulted in increased postoperative in-hospital mortality than surgery alone (Fiorica et al., 2004), due to the three most frequent adverse events of respiratory complications, heart failure, and anastomotic leakage (Fiorica et al., 2004). As discussed in the General Considerations section, 3-field LND realizes local control, so that neoadjuvant CTx can afford a most impressive survival advantage and be regarded as a new standard regimen in stage II/III squamous cell carcinoma in Japan.

4.3 Definitive CRTx for resectable EC

CRTx only (definitive CRTx) undoubtedly represents an alternative treatment for patients with EC considered unsuitable for surgery on the basis of comorbidity, poor performance status, and locoregional diseases too extensive for curative resection. For respectable EC, although esophagectomy has still been designated as -at least a part of- a pivotal treatment modality, it is indeed a complex, highly invasive procedure. Operative morbidity and mortality undoubtedly depend on hospital volume; however, reports on this topic from the West, some of which were from high volume centers, documented a near 50% morbidity and 10% mortality (Bailey et al., 2003; Birkmeyer et al., 2002; Jamieson et al., 2004). Since CRTx does have a significant downstaging effect but increases postoperative mortality when combined with surgery, there is growing enthusiasm for the definitive CRTx to treat potentially resectable EC. The choice of CRTx as a definitive treatment option is based on the RTOG 8501 trial, which was instrumental in defining the superiority of definitive CRTx with a 50Gy radiation dose over definitive 64Gy RTx alone (Herskovic et al., 1992). A subsequent metaanalysis has confirmed its promise (Wong & Malthaner, 2006).

Two large RCTs examined whether surgery was necessary after CRTx. A German group demonstrated similar 2-year SR in the neoadjuvant CRTx to a total dose of 40Gy followed by surgery (40%), and in the definitive CRTx with at least 65Gy (35%) in locally advanced squamous cell cancer (Stahl et al., 2005). A subsequent French trial (FFCD9102) (Bedenne et al., 2007; Bonnetain et al., 2006) also confirmed no benefit for additional surgery after CRTx to the responding patients with locally advanced squamous cell cancer. In addition, a nonrandomized comparison revealed the same impact on survival between definitive CRTx and surgery only (without adjuvant treatment) (Hironaka et al., 2003). A single arm phase II study in Japan (JCOG9906) (K. Kato et al., 2010) demonstrated that definitive CRTx in stage II/III esophageal squamous cell cancer could yield a complete response rate of 62%, with 3-year and 5-year SR being 45% and 37%, respectively, comparable to those for esophagectomy (33-47% and 20-52%, respectively) (The Japan Esophageal Society). However, these findings are still inferior to those of the neoadjuvant CF arm in the JCOG 9907 trial. Accordingly, definitive CRTx is not regarded as a standard treatment for stage II/III esophageal squamous cell cancer in Japan.

Nevertheless, these encouraging reports have led to the further activation of several studies to assess the efficacy of definitive CRTx for patients with earlier stage squamous cell cancer. JCOG9708 trial (H. Kato et al., 2009) elucidated 2-year and 4-year SRs of 93% and 81%, respectively, which were comparable to those of the stage I SCC undergoing esophagectomy (The Japan Esophageal Society). Other investigators also reported a high complete response rate (88%) and 3-year SR (79%) in patients with stage I SCC by definitive CRTx (Minashi et al., 2006). However, definitive CRTx is accompanied by several problems.

First, and unfortunately, crude locoregional control rates remain poor, with a respective 23-65% and 13-67% of patients having persistent disease or relapse at the primary site (Coia et al., 2000; Cooper et al., 1999; Minsky et al., 2002; Murakami et al., 1998; Stahl et al., 2005; K.S. Wilson & J.T. Lim, 2000). Tumor recurrence among patients whose treatment results deemed CR is a problem with definitive CRTx because no perfect diagnostic methods currently exist for the evaluation of CR. In the JCOG 9708 trial, although the complete response rate was high (88%), half of the total patients relapsed. In another definitive CRTx trial (Minashi et al., 2006), locoregional diseases were discovered later in 14 (39%) of 36 complete response patients. Although surgery is not intended as part of the definitive CRTx,

salvage surgery that could offer the only chance of cure for patients with recurrent or residual diseases after definitive CRTx should be considered. In addition, definitive CRTx-related local complications such as esophageal stenosis and perforation are also indications for salvage surgery. However, salvage surgery is a highly invasive and complex treatment leading to increased morbidity (50-79%) and in-hospital mortality (7-22%) as compared with those after neoadjuvant CRTx, due to the adverse events of predominantly respiratory complications and anastomotic leakage (Chao et al., 2009; Nakamura et al., 2004; M. Nishimura et al., 2007; Oki et al., 2007; Smithers et al., 2007; Swisher et al., 2002; Tachimori et al., 2009; Tomimaru et al., 2006). These hospital mortality rates are obviously higher than those for esophagectomy in Japan reported from specialized centers (2%) (Tachimori et al., 2009) or the nationwide registry (5%) (The Japan Esophageal Society). Second, definitive CRTx for resectable EC has the merit of preserving the esophagus, though it may increase late toxicity such as pericardial or pleural effusion (Ishikura et al., 2003; Kumekawa et al., 2006). Pericardial and pleural effusion developed in nearly 20% of complete response patients, leading to 10-12% of treatment-related deaths (Ishikura et al., 2003; Kumekawa et al., 2006). Even in the earlier stage squamous cell cancer, definitive CRTx-related mortality was observed in 8% of complete response patients (Minashi et al., 2006). These facts suggest that late toxicities are often progressive in severity and may compromise the long term health-related quality of life of a cancer survivor, leading to nullifying the anticipated treatment benefit from therapy. Since conventional toxicity reporting tends to present the more intensive treatments as less toxic than they really are (Trotti et al., 2007), one should bear in mind that the actual toxicities are likely to be underestimated.

These complications are accounted for by the radiation *per se* that renders risks of pulmonary complications, partly due to the fibrogenic response pathway (Bentzen, 2006), and the radiation induced injury in the thoracic cavity that makes surgical procedures technically more difficult and subsequently increases bleeding. In addition, the irradiated stomach, esophagus, and trachea become fragile with the impaired blood supply that eventually causes anastomotic leakage or conduit necrosis. The incidences of morbidity after salvage surgery were associated with radiation doses rather than clinical factors (Wang et al., 2006), suggesting that a dosimetric aspect should be taken into account in planning a definitive CRTx. On this basis, several attempts have been made to reduce the incidences of postoperative morbidity and mortality of salvage surgery. RTOG94-05/INT0123 elucidated the possibility of total radiation volume reduction (50.4Gy), which was equally effective as compared with higher doses (64.8Gy) (Minsky et al., 2002). A novel radiation technique has been developed to ensure an increased volume of lung unexposed to radiation to deliver large and uniform doses to the tumor while sparing nearby normal tissues (X. Zhang et al., 2008). In Japan, based on the phase I study results (T.E. Nakajima et al., 2009), a phase II study of definitive CRTx with a radiation dose of 50.4Gy for stage II/III esophageal squamous cell cancer is ongoing (JCOG0909). In planning a definitive CRTx, therefore, a higher radiation dose is not recommended because it does not improve survival but would presumably increase the risks of salvage surgery if needed.

Given the highly invasive and formidable procedures of salvage surgery, patient selection of those who would receive the most benefit or who would be unfit for surgery is a major concern in the clinical field. Several factors have been proposed for patient selection for salvage surgery. First, there is some evidence that patients with recurrence after CRTx had a significantly better survival after salvage surgery than those with persistent disease (Swisher et al., 2002). Salvage surgery could be avoided in complete response patients, but the

diagnosis of complete response by imaging is not always reliable and is possible merely by resected specimen. Indeed, 10-13% of patients undergoing salvage surgery were proved to have pathologically complete response (Murakami et al., 1998; M Nishimura et al., 2007; Tachimori et al., 2009). Unfortunately, positron emission tomography using 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (FDG-PET) (Klaeser et al., 2009) or its combination with other imaging modalities such as computed tomography and/or endoscopic ultrasonography (Swisher et al., 2004) failed to distinguish between patients with >10% viable cells and those with <10% viable cells, resulting in a false negative rate of 16-31% by each modality (Swisher et al., 2004). In this study, the accuracy rates decreased dramatically when an attempt was made to distinguish microscopic residual disease (1% to 10% viable cell) from the "true" pathological complete response (0% viable cells), implying that these modalities have limited value for response assessment for patients receiving preoperative treatment. Consequently, patients whose tumor response is deemed complete response after CRTx could have residual diseases and not be ascribed a reason to preclude further additional treatment. To solve these drawbacks, recent research has focused on the gene expression that can predict CRTx response (Eschrich et al., 2009; He et al., 2009; Maher et al., 2009). Second, multivariate analysis revealed that the most significant factor associated with long-term survival was a R0 resection (Chao et al., 2009; Tomimaru et al., 2006). No patients left with gross or microscopic residual tumors after salvage surgery (R1/R2 resections) survived more than 24 months in any series (Chao et al., 2009; Nakamura et al., 2004; Oki et al., 2007; Swisher et al., 2002; Tachimori et al., 2009; Tomimaru et al., 2006). However, the R1/R2 resection rate has been substantially high, ranging from 15-50% (Chao et al., 2009; Nakamura et al., 2004; Oki et al., 2007; Swisher et al., 2002; Tachimori et al., 2009; Tomimaru et al., 2006), and the resection status cannot be confidently predicted before surgery or even during surgery because of the indistinct planes between tumor and fibrotic masses within the irradiated mediastinum. Therefore, FDG-PET or other imaging modalities are used to select patients who are absolutely unfit for salvage surgery. There is an urgent need for the development of more reliable, accurate diagnostic tools for the assessment of response and resection status prediction.

5. Molecular targeting therapy

Despite the many challenges for establishment of more active multimodal therapy regimens, the mean average survival benefit remains only slight in GC and EC. The MST remains consistently around or less than 12 months in metastatic GC and EC (Ishida et al., 2004; Koizumi et al., 2008; Y. Nishimura et al., 2002; Ohtsu et al., 1999), underscoring a need for more active new agents and regimens. Against these backgrounds, a new generation of therapies designed to target epidermal growth factor receptor (EGFR) and subsequent cellular responses, or angiogenic processes, which both involve and promote tumor growth and survival, have been very recently introduced.

There are several approaches to target EGFR or angiogenic processes. First is monoclonal antibodies against EGFR, including cetuximab (a chimeric monoclonal immunoglobulin G1 antibody), panitumumab (a fully human monoclonal immunoglobulin G2 antibody), and trastuzumab (a monoclonal antibody against human epidermal growth factor receptor-2 (HER2)). Second is an inhibition of the tyrosine kinase (TK) domain and subsequent signal cascade; the molecules which play the role include gefitinib, erlotinib (both are inhibitors of EGFR-TK), lapatinib (a dual inhibitor of HER2-TK and EGFR-TK), sunitinib (inhibitor of TK

of various kinds of proteins), and everolimus (RAD001) (inhibitor of mammalian target of rapamycin). Third is an inhibitor of tumor vascularization to anticipate the prevention of eventual tumor invasion and metastasis such as bevacizumab, a monoclonal antibody developed to target vascular endothelial growth factor (VEGF). There are several planned or ongoing RCTs incorporating molecular targeting therapies, and some trials have provided encouraging results.

5.1 Anti-EGFR antibody

A positive HER2 protein or amplified HER2 gene was observed in approximately 20% of GC patients (Jørgensen, 2010). An efficacy of trastuzumab for GC has been very recently demonstrated by a global RCT (ToGA trial; NCT01041404) which has revealed a significantly ($p<0.005$) prolonged MST (13.8 months) and RR (47%) by adding trastuzumab to 5FU (or capecitabine) and cisplatin as compared with those (11.1 months and 35%) without trastuzumab (Bang et al., 2010). However, it should be noted that the RR by adding trastuzumab to CTx was at best 50% even among the HER2 positive GC patients. Furthermore, the improvement of MST (13.8 months) was -although promising- only marginal as compared with those of a CS in SPIRITS trial (Koizumi et al., 2008). Furthermore, subanalysis by region revealing the efficacy of adding trastuzumab was observed in Europe and Central/South America but not in Asia. Considering that second-line treatment was performed more in Asia than in Europe or Central/South America, the power of second-line therapy in the control (without trastuzumab) arm may bring the treatment results of the two arms closer, leading to non-significant results in Asia.

5.2 Anti-VEGF antibody

The AVAGAST trial (NCT00548548) is the first RCT investigating the efficacy of bevacizumab, in which GC patients were randomized to 5-fluorouracil (or capecitabine) and cisplatin with or without bevacizumab (Y. Kang et al., 2010). Adding bevacizumab achieved a longer PFS (6.7 months vs. 5.3 months) and higher overall RR (38% vs. 30%); however, it failed to produce significant MST prolongation (12.1 months vs. 10.1 months). Several explanations are possible for these negative results. The results appeared to differ among subgroups according to geographic region. As was seen in the ToGA trial, adding bevacizumab proved to be effective in the pan-American region and in Europe but not in Asia, reflecting the role of a second-line treatment (van Cutsem et al., 2010). Alternatively, a potential disadvantage of the AVAGAST trial is a lack of a specific target that would allow for the optimal patient selection that was possible in the ToGA trial.

6. Future perspectives

While many regimens incorporating multimodal therapies have been investigated, it is also true that there is a great variability in tumor response and patient survival among regimens. In addition, even among patients receiving the same regimen, a given regimen may prove too active or too toxic for an individual. Unfortunately, however, it is difficult to predict perfectly the efficacy and toxicity prior to therapy. Therefore, there is a pressing need to explore the molecules and genes that could help explain the interindividual differences in drug response and toxic events. Such a discovery and validation of predictive biomarkers could allow us to develop a model for selecting the optimal therapy on an individual basis

and reduce morbidity and reduce health care costs by avoiding potentially unnecessary or futile treatment, ultimately allowing treatment to be individualized (Shimoyama, 2009).

One example is a predictive role of a biomarker in the usage of anti-EGFR therapy. Since mutant K-Ras or mutant B-Raf causes cells to escape from adequately controlled cell proliferation and consequently confers resistance to anti-EGFR therapies, K-Ras (Lièvre et al., 2008) or B-Raf (Tol et al., 2009) is considered a negative predictor for the efficacy of anti-EGFR therapy such as cetuximab and panitumumab in colorectal cancer (Allegra et al., 2009; Amado et al., 2008; Jiang et al., 2009). In contrast, incidences of K-Ras mutation were 3-21% in GC (Hongyo et al., 1995; I.J. Kim et al., 2003; Lee et al., 2003; Yoo et al., 2002; W. Zhao et al., 2004) and 0-9% in EC (Janmaat et al., 2006; Lorenzen et al., 2009), both relatively low as compared with those of colorectal cancer (Andreyev et al., 1998). In addition, the predictive value of the K-Ras mutation concerning the efficacy of anti-EGFR therapy has not been clearly established in esophagogastric cancer (Park et al., 2010). Furthermore, incidences of B-Raf mutation in GC were also low (2.2-3%). Therefore, whether mutations of K-Ras or B-Raf as negative predictors seen in colorectal cancer can be extrapolated into gastric and esophageal cancers requires further study. Actually, current phase III trials of cetuximab or panitumumab in GC and EC allow the inclusion of patients irrespective of K-Ras mutation status or EGFR immunohistochemical positivity. In addition, since racial difference does exist in some drug metabolizing enzymes (Shimoyama, 2010), the usefulness of predictive biomarkers may differ between Western and Eastern hemispheres as well as between tumor types.

Another perspective is the incorporating of molecular targeting therapy or other agents into conventional therapy. As discussed in the INT0116 trial, new generation agents with radiosensitizing effects should be continuously incorporated into future clinical trials. Accordingly, several promising results have been reported by the use of new generation agents in combination with molecular targeting therapy, or with radiation, or both (Gaast et al., 2010; Knox et al., 2010; Pinto et al., 2007; Safran et al., 2008; Spigel et al., 2010; Syrigos et al., 2008). Furthermore, non-cytotoxic agents such as statins are theoretical candidates for overcoming current problems of molecular targeting therapy (Shimoyama, 2011).

It is impossible to conduct RCTs for exhaustive drug combinations. There must be continuing efforts to obtain knowledge on specific drug interactions that could bypass clinical trials from one administration schedule to another or from one tumor type to another. This stance may most efficiently facilitate the establishment of the best multimodal therapies.

7. Conclusion

In GC, recent RCTs have elucidated the promising efficacy of multimodal therapies in an adjuvant and advanced settings, where S-1 plays a pivotal role in these settings. This is in agreement with the recent stance in which oral administration takes advantage over the intravenous administration. In EC, CRTx in neoadjuvant or definitive setting has gained the most intensive research topic; however, the latter setting is inevitably associated with highly morbid salvage surgery. Furthermore, researches in novel targeted therapies against growth signal transduction cascade have just begun and their efficacy has been anticipated.

For the treatment of GC and EC, we should say “good-by” for the surgery only treatment era while the “multimodal treatment era” is welcomed. It is hugely encouraged to consider

multimodal therapies on the adjuvant, neoadjuvant, and advanced settings, as well as by the usage of conventional treatment (CTx, RTx, and CRTx) and targeted therapies, alone or in combination. Recent attempts have continuously clarified the molecular profiles or genetic events to stratify patients who receive the best benefit, which realizes maximization of the treatment effects instead of "one-regimen-fits-all" stance.

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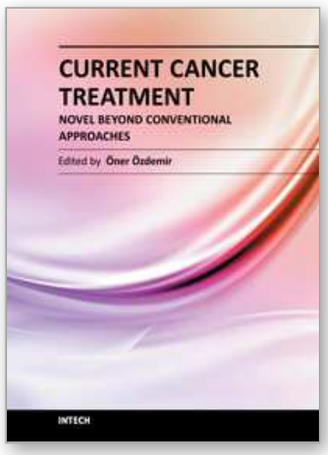

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Currently there have been many armamentaria to be used in cancer treatment. This indeed indicates that the final treatment has not yet been found. It seems this will take a long period of time to achieve. Thus, cancer treatment in general still seems to need new and more effective approaches. The book "Current Cancer Treatment - Novel Beyond Conventional Approaches", consisting of 33 chapters, will help get us physicians as well as patients enlightened with new research and developments in this area. This book is a valuable contribution to this area mentioning various modalities in cancer treatment such as some rare classic treatment approaches: treatment of metastatic liver disease of colorectal origin, radiation treatment of skull and spine chordoma, changing the face of adjuvant therapy for early breast cancer; new therapeutic approaches of old techniques: laser-driven radiation therapy, laser photo-chemotherapy, new approaches targeting androgen receptor and many more emerging techniques.

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