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Review Article: Molecular Target Treatment

Current Status and Problems in Development of Molecular Target Agents for Gastrointestinal Malignancy in Japan

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Since late 1990s, many molecular target agents have been introduced to clinical trials for various kinds of tumors, and some of them showing significant benefits have been approved. However, these global trials were mainly conducted outside Japan, and the 'drag lag' has been a serious problem in Japan recently. Nowadays, Japanese institutions have been participating in some global trials, and the drug lags are getting shorter. For colorectal cancer, molecular target agents such as bevacizumab and cetuximab have been approved in Japan, resulting in improved clinical outcomes. For gastric cancer, Japanese institutions not only contribute to the global Phase III trials of trastuzumab and bevacizumab but also show leadership in the early development of other new agents. For pancreatic cancer, only erlotinib has shown a survival benefit in these 10 years. Worldwide approach including Japan is warranted to achieve better clinical outcomes. For liver cancer, although Japanese institutions did not participate even in the Asian trial of sorafenib, it has been approved in Japan. For esophageal cancer, because there has been no new molecular target agents developed by pharmaceutical companies, investigator-initiated registration trial will play an important role. For all gastrointestinal malignancies, molecular target agents have made a progress in their treatments. In the near future, Japanese institutions will participate in more and more global trials and should play a specific role in worldwide drug development. Furthermore, the optimal use of these new drugs, molecular target agents, based on the daily practice should also be explored in Japan.

Key words: development – molecular target agent – gastrointestinal malignancy

INTRODUCTION

Since late 1990s, many molecular target agents have been introduced to clinical trials for various kinds of tumors, and some of them showing significant benefits have been approved. Actually, molecular target agents have made a remarkable progress in treatment of gastrointestinal malignancies and been widely used in clinical practice worldwide. In the past, the global trials were conducted mainly outside Japan, and thereafter independent studies, mainly Phase II, were added for registration in Japan after approval in Western countries. These independent registration trials caused the 'drag lag', and it has been a serious problem in Japan recently. After the guideline regarding to clinical evaluation of drugs for malignant disease was revised, Phase III trials are mandatory for common malignancies such as lung, gastric, colorectal, liver and breast cancers, whereas data of clinical trials conducted overseas are acceptable in Japan. Nowadays, many pharmaceutical companies have been including Japanese institutions in global clinical trials. However, there are merits and problems in these development and approval methods, depending on cancer types and developing stages. Furthermore, there should be roles for Japanese institutions to play from the global point of view as a part of ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use).

COLORECTAL CANCER

Until recent days, chemotherapy for metastatic colorectal cancer in Japan was far behind from Western countries, not

only with molecular target agents but also with cytotoxic agents. Until 2004, in Japan, the most active regimen had been IFL (1) which comprised bolus 5-fluorouracil (5-FU)/leucovorin and drip infusion of irinotecan (CPT-11) even after N9741 trial showed that FOLFOX, which is based on infusional 5-FU and combination with oxaliplatin, regimen showed a survival benefit over IFL (2). Although CPT-11 was approved for colorectal cancer in 1994, 2 years earlier than the USA, delay in approval of leucovorin (1999), oxaliplatin (2005) and infusional 5-FU with leucovorin (2004) had been limiting clinical practice for metastatic colorectal cancer in Japan (Table 1). It seemed to be unusual that oxaliplatin in combination with infusional 5-FU was approved without any data of FOLFOX regimens in Japanese population.

Recently, molecular target agents such as bevacizumab (3–5) and cetuximab (6–8) have been playing an important role for managing patients with metastatic colorectal cancer. Bevacizumab added to IFL regimen showed a remarkable survival benefit over IFL alone (3), in the first-line chemotherapy and so did it in the second-line chemotherapy combined with FOLFOX regimen (5). In Japan, only one study investigating its feasibility in combination with XELOX regimen was conducted for registration. As a result, the approval of bevacizumab was delayed by 3 years compared with the USA. Cetuximab showed a survival benefit in the third line compared with best supportive care (6), and longer progression survival time in combination with FOLFIRI and CPT-11 in the first (7) and second lines (8), respectively. In Japan, after its Phase I studies of monotherapy (9) and combination therapy with CPT-11 (10) had been conducted, it was approved in 2008, 4 years later than the USA. Although it has been widely accepted that cetuximab shows no activity to the patients whose tumors has K-ras mutation (11), the K-ras mutation test has not been approved in Japan.

Until early 2000, the drug lag between Japan and Western countries had been awfully large, and recently, it has been getting shorter. Now, some Japanese patients are enrolled to the global Phase III studies investigating new drugs to get approval worldwide. However, Phase I studies are still delayed from global ones, and it seems obligate to reach the same target dose in Japanese Phase I studies, although there might be ethnic differences in feasibility. In the near future, Phase I studies of new drugs should be started simultaneously also in Japan.

In conclusion, chemotherapy for colorectal cancer in clinical practice in Japan has caught up with Western countries while there has been no recent progress globally (12). Japanese institutions should participate in the development of new drugs from the early stages.

Table 1. Drug approval for colorectal cancer in Japan and in the USA

Agents	Approval	
	Japan	USA
5-FU/leucovorin	1999	1980s
Irinotecan	1994	1996
Capecitabine	2007	2001
Oxaliplatin	2005	2002
Cetuximab	2008	2004
Bevacizumab	2007	2004

5-FU, 5-fluorouracil.

GASTRIC CANCER

In spite of the several reports of Japanese large Phase III trials (13–15) for advanced gastric cancer which has established a standard chemotherapy in Japan, they have only a little impact worldwide because they contained S-1 which did not show a survival benefit over 5-FU combined with cisplatin (CDDP) in FLAGS trial (16). Therefore, the standard practice for advanced gastric cancer in Japan is a little bit different from that in Western countries, where capecitabine and/or oxaliplatin has been used widely. Although neither of these new drugs is approved in Japan, we should accept the control arm based on capecitabine in the global Phase III trials.

Although clinical trials for gastric cancer were conducted separately between Asian and Western countries in 1990s, the number of global studies focusing on gastric cancer which include both Asian and Western countries has been remarkably increasing. ToGA trial (17), which showed a survival benefit of trastuzumab added to combination chemotherapy with 5-FU (capecitabine or continuous infusion of 5-FU) and CDDP for the patients with Her-2-positive gastric cancer, is the first global study to which many Japanese patients with gastric cancer were enrolled. Because the frequency of Her-2-positive gastric cancer is reported to be around 20% among all gastric cancers (18), it was necessary to screen very large number of patients ($n = 3807$) for enrollment. Asian countries where the incidences of gastric cancer are high play an important role for this study, and actually, Korea and Japan were the first and the second contributors. As for bevacizumab, the enrollment to the Phase III study, comparing between combination chemotherapies with and without bevacizumab based on the 5-FU (capecitabine or continuous infusion of 5-FU) plus CDDP, has been completed, and the final results are planned to be published in 2010. Japanese institutions enrolled the most patients to this study all over the world. Now, there are three global Phase III trials on-going, in which cetuximab (19) for the first line, lapatinib (20) for the second line and everolimus (21) compared with best supportive care are investigated.

As for the early development of molecular target agents for gastric cancer, there are many Phase I and II trials both in monotherapy and in combination chemotherapy conducted in Japan such as nimotuzumab (22) (EGFR inhibitor), axitinib (23), cediranib (24), sunitinib (25), aflibercept (26) (angiogenesis inhibitor), heat shock protein inhibitor, c-met

inhibitor, insulin-like growth factor inhibitor and so on (Table 2). Among them, the Phase I and II studies of everolimus were initiated in Japan, and now they have proceeded to the global Phase III trial.

In conclusion, Japan has become one of leaders contributing not only to global Phase III studies but also to the early development of molecular target agents for gastric cancer.

PANCREATIC CANCER

Since gemcitabine (GEM) showed a survival benefit over 5-FU alone (27), it has been a standard care for advanced pancreatic cancer worldwide. In Japan, GEM was approved only after a Phase I study of a very small number of patients (28). Although several Phase III trials investigating combination chemotherapies of GEM with other drugs, including molecular target agents (Table 3) such as bevacizumab (29) and cetuximab (30), were conducted, only erlotinib (tyrosine kinase inhibitor of EGFR) showed a modest survival benefit (31). It was after getting the result of this Phase III when a Phase II trial of combination chemotherapy with GEM and erlotinib was started in Japan. Furthermore, pneumonitis due to this combination chemotherapy is considered to be a big problem in Japan, although there are no differences in its incidence and severity (32).

Recently, Japan was the second contributor to enrollment of patients to the Phase III trial comparing GEM plus axitinib with GEM alone. Although axitinib could not unfortunately show a survival benefit (33), this trial was the first global Phase III trial that many Japanese patients with pancreatic cancer were enrolled. Although the potential of patient accrual from Japan was demonstrated in the axitinib study, Japanese institutions have been participating to none of the other global Phase III trials since then.

During the similar period to the global Phase III of erlotinib, a Phase II studies of S-1 (34) with and without GEM (35) showed very promising results, and a Phase III trial with two pair comparisons investigating the non-inferiority of S-1 and the superiority of S-1 plus GEM to GEM alone has been conducted in Japan. If the combination chemotherapy of S-1 plus GEM could show a survival benefit over GEM alone, S-1 plus GEM would be a new standard care for advanced pancreatic cancer at least in Japan. Then, however, because S-1 is not accepted worldwide, it is afraid that difference in the standard care might make it more difficult for Japanese institutions to participate in the future global trials based on the monotherapy with GEM.

In 2008, CONKO group reported the results of Phase III trial comparing between infusional 5-FU with and without oxaliplatin in the second-line setting after failure in GEM (36), resulting in a longer survival with oxaliplatin. And NCCN guideline adopted this therapy in the second-line setting after failure in GEM. In Japan, a Phase III study comparing S-1 plus oxaliplatin with S-1 is underway.

In conclusion, the introduction of new drugs to Japan has been delayed in spite of the fact that there has been no progress except for erlotinib. Although there is no difference in the incidence of pancreatic cancer between Japan and Western countries, worldwide collaboration is warranted for the development of new drugs for advanced pancreatic cancer.

Table 2. Clinical trials of molecular target agents for gastric cancer in Japan

Agent	Mechanism	Phase	Combination
Gefitinib	TKI of EGFR	Stop	—
Lapatinib	TKI of Her-1,2	III	Paclitaxel
Nimotuzumab	MoAb to EGFR	rII	Irinotecan
Cetuximab	MoAb to EGFR	III	Capecitabine + cisplatin
Trastuzumab	MoAb to Her-2	III	Capecitabine + cisplatin
Bevacizumab	MoAb to VEGF	III	Capecitabine + cisplatin
Aflibercept	VEGF trap	I	S-1
Sunitinib	Multiple TKI	I	S-1 + cisplatin
Cediranib	TKI of VEGFR	I	S-1/capecitabine + cisplatin
Everolimus	mTOR inhibitor	III	—
TSU-68	TKI of VEGFR	rII	S-1 + cisplatin
ARQ197	cMET inhibitor	II	—
Sorafenib	Raf inhibitor	I	S-1 + cisplatin

TKI, tyrosine kinase inhibitor; EGFR, epidermal growth factor receptor; MoAb, monoclonal antibody; VEGF, vascular endothelial growth factor; mTOR, mammalian target of rapamycin.

Table 3. Recent Phase III trials of molecular target agents for pancreatic cancer

Regimens	*n*	MST (months)	*P* value
GEM + marimastat	120	5.4	0.95
GEM	119	5.4	
GEM + tipifarnib	334	6.3	0.75
GEM	342	6.0	
GEM + erlotinib	285	6.2	0.04
GEM	284	5.9	
GEM + cetuximab	369	6.4	0.14
GEM	366	5.9	
GEM + bevacizumab	302	6.1	0.78
GEM	300	5.8	
GEM + erlotinib + bevacizumab	306	7.1	0.21
GEM + erlotinib	301	6.0	

MST, median survival time; GEM, gemcitabine.

LIVER CANCER

Treatment of liver cancer [hepatocellular carcinoma (HCC)] comprises multimodality such as resection (transplantation), ablation, trans-arterial chemo-embolization (TACE) and

systemic chemotherapy, and treatment selection seems to be difficult and complicated according to the liver function, number, sites and size of tumors. Furthermore, it was considered that HCC is not sensitive to cytotoxic agents because of their low response rates and substantial toxicities due to liver dysfunction.

Recently, systemic chemotherapy for HCC has entered the new era, molecular target agents. In SHARP trial conducted in Western countries, sorafenib showed a survival benefit over best supportive care in the patients with HCC who were not indicated local therapies (37). It is well known that the etiology of HCC differ between Asian and Western countries. The Asian Phase III trial (38) was also conducted, showing similar results to those of SHARP trial. However, Japanese institutions did not participate in this Asian trial and conducted a clinical trial of sorafenib following TACE in Japan. Sorafenib was approved before the result of the Japanese trial was disclosed.

Nowadays, while a couple of global clinical trials investigating molecular target agents, such as sunitinib and RAD001, for HCC, Japanese institutions do not participated in them. In fact, Asian doctors outside Japan say that Japanese patients seem to be different in the etiology, hepatitis virus B and C, in anti-viral therapy and in basic liver function, it is extremely afraid that Japan might be isolated in the clinical trials for HCC.

In conclusion, the role of systemic chemotherapy with new molecular target agents is getting larger and larger for HCC. Although other Asian countries contribute to development of them, Japanese institutions should also participate in global trials for HCC.

ESOPHAGEAL CANCER

Multimodality treatment is generally performed for resectable esophageal cancer worldwide. Recent clinical trials have been focusing on treatment strategy such as comparison between neoadjuvant and adjuvant chemotherapy (39), between with and without neoadjuvant chemoradiation therapy (40), and between definitive and neoadjuvant chemoradiation therapy (41). In Japan, JCOG9907 trial (39) showed that neoadjuvant chemotherapy followed by surgery resulted in a 5-year survival rate about 60% higher than adjuvant chemotherapy, whereas definitive chemoradiation therapy whose 5-year survival rate was 37% (JCOG9906) (42). Thus, it is considered that chemoradiation therapy have some problems: (i) poor local control and (ii) late radiation toxicities. New drug development is a key to solve the problem of efficacy. However, there have been very few new drugs developed for esophageal cancer, and 5-FU and CDDP have been still key drugs for a long time.

The reluctance of pharmaceutical companies to new drug development for esophageal cancer is caused by a low incidence of the disease, complicated multimodality treatment and severe adverse events. Thus, investigator-initiated registration trial is underway, such as cetuximab in RTOG and S-1 in JCOG (Japan Clinical Oncology Group). It seems extremely hard for Japanese institutions to participate in the RTOG study because they have to satisfy both Japanese regulation (Good Clinical Practice) and RTOG requirement by themselves. Furthermore, the majority of esophageal cancers in Japan are squamous cell carcinoma histologically, whereas more than half in Western countries were adenocarcinoma. Therefore, it is afraid that the evidence established in Western countries may not be introduced to Japan directly.

In conclusion, new drugs including molecular target agents have been hardly developed worldwide as well as in Japan.

CONCLUSION

Recent development of molecular target agents has made a progress in the treatment of gastrointestinal malignancies, resulting in better clinical outcomes. Japanese institutions should participate in global trials to eliminate drug lag and has to play a specific role in worldwide drug development from the point of ICH. Furthermore, because these trials aim to the approval of new drugs based on the global standard, their optimal use based on the daily practice should also be explored in Japan.

Conflict of interest statement

None declared.

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