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An Overview on Recent Progress of Anti-Cancer Agents

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This overview deals with the recent progress of anti-cancer agents from the point of view of developing both cytotoxic agents and agents acting on novel molecular targets, often referred to as cytostatic agents, in the last decade in Japan and in U.S.A. Because there are a number of anti-cancer agents that have been developed against various types of cancers, anti-cancer agents against advanced colorectal cancer and lung cancer, which cancers are two of the leading causes of cancer deaths in Japan as well as in the Western world, are especially focused in this overview.

Cancer treatment, outside of surgery, has been dominated over the past 40 years by the use of cytotoxic chemotherapeutic drugs and radiation therapy, unfortunately with rather limited success.

Table. Chronology of treatment options for advanced colorectal cancer

1960s:	5-fluorouracil (5-FU)
1980s:	Modulated 5-FU (biochemical modulation with leucovorin)
1990s:	Infusional 5-FU
	New cytotoxic agents: irinotecan, oxaliplatin, and oral fluoropyrimidines
2000:	Agents acting on novel molecular targets
	Molecular/surrogate marker

Until the early 1990s, therapeutic options for advanced colorectal cancer were mainly confined to chemotherapy with 5-FU in various schedules, with or without biochemical modulation with leucovorin (LV). The treatment of patients with metastatic colorectal cancer has changed dramatically over the last ten years. The more optimal use

of 5-FU in association with LV, the new drugs such as irinotecan and oxaliplatin, or the oral fluoropyrimidines capecitabine and uracil/tegafur (UFT) have contributed to the increased therapeutic options and to the improved outcome of patients with metastatic colorectal cancer. CPT-11, or irinotecan, is a campothecin analog that inhibits DNA topoisomerase I and induces single-strand DNA breaks and replication arrest. Oxaliplatin is a third-generation platinum analog that induces DNA cross-linkages and apoptotic cell death. It has been shown that combination therapy with 5-FU/LV and irinotecan or oxaliplatin is more effective than 5-FU/LV in first-line treatment of advanced colorectal cancer. Many clinicians have accepted that combination treatment is a standard option in first-line treatment of advanced colorectal cancer. Irinotecan and oxaliplatin are also active in patients refractory to 5-FU/LV. The oral fluoropyrimidines capecitabine and UFT/LV also seem to have comparable activity to intravenous bolus 5-FU/LV in first-line treatment of metastatic colorectal cancer. UFT is a combination of uracil and tegafur (a prodrug of 5-FU) in a fixed molar ratio of 4:1. Uracil is a normal substrate for dehydropyrimidine dehydrogenase and competitively blocks the action of this enzyme, allowing tegafur absorption and the availability of biologically active plasma concentration of 5-FU. UFT is usually administered with oral leucovorin. Capecitabine, a fluoropyrimidine carbamate, is a prodrug that can be absorbed through the intestinal mucosa and is converted to 5-FU via three enzymatic steps[1, 2].

Many new agents are in preclinical or early clinical development for colorectal cancer. It is expected that agents acting on novel targets will play an important role in the future treatment of colorectal cancer. A few examples of classes of new agents under development are the epidermal growth factor receptor (EGFR [HER-1]) inhibitors, Ras farnesyltransferase inhibitors, the vascular endothelial growth factor (VEGF) receptor inhibitors, and cyclooxygenase-2 (COX-2) inhibitors.

Epidermal growth factor (EGF) is an important signaling pathway that promotes mitogenesis, invasion, and angiogenesis. EGFR inhibitors under development are the

monoclonal antibody IMC-C225 (cetuximab) and the EGFR tyrosine kinase inhibitors erlotinib (OSI-774) and gefitinib (ZD1839, Iressa). The EGFR is also expressed or overexpressed in most non-small-cell lung cancers (NSCLCs). These agents also cause objective regression and improve symptoms in patients with NSCLC as well as with colon cancer that is refractory to cytotoxic chemotherapy. In preclinical studies, combining EGFR inhibitors such as cetuximab (IMC-C225) or ZD1839 with cytotoxic chemotherapy or irradiation produced additive or synergistic effects[3, 4].

In the case of metastatic breast cancer, trastuzumab (Herceptin), a humanized monoclonal antibody to overexpressed receptor tyrosine kinase erbB2/HER-2/neu showed a synergistic antitumor effect in combination with paclitaxel[5]. Herceptin has provided the first proof that tyrosine kinase modulation, through monoclonal antibodies, can translate into improved clinical outcome in cancer therapy. The development of Herceptin was encouraged by the biologic significance of HER-2 overexpression.

Concerning topics on selective tyrosine kinase inhibitors, it should be added that chronic myelogenous leukemia (CML) is a clonal myeloproliferative disorder molecularly defined by the BCR-ABL gene and its products. The protein encoded by this chimeric gene is a constitutively activated tyrosine kinase that alters multiple signal transduction pathways inducing malignant transformation. Thus, the BCR-ABL tyrosine kinase is an ideal target for pharmacological inhibition. STI571 (Gleevec) is an ABL-specific inhibitor of tyrosine kinase that, in preclinical studies, selectively killed BCR-ABL-containing cells in vitro and in vivo. Clinical studies have shown the potential of this specifically targeted therapy, and STI571 is emerging as an important new therapeutic agent for CML.

Many growth factors activate Ras as an early event in their signal pathways, and Ras is therefore an important target for both colon and lung cancer therapy.

The Ras protein resides in a cytoplasmic location in its inactive state. Ras requires protein farnesylation to become active and to bind to the cell membrane. Thus,

farnesyltransferase inhibitors (FTIs) have become novel agents for therapy. Several types of FTIs have been developed, including peptidemimetics and nonpeptidemimetics. Interestingly, several of these inhibitors were able to inhibit the growth of colon and lung cancer cell lines irrespective of the presence or absence of *ras* mutations. Preclinical studies have shown that FTIs inhibited the growth of human colorectal tumor and lung tumor xenografts in athymic nude mice as well as in cell culture. Preclinical studies have also shown that FTIs could prevent the development of colon tumor or lung tumor in mouse carcinogenesis models.

The critical signaling role of Ras may explain the activity of FTIs. Alternatively, other proteins involved in oncogenesis require farnesylation and their inhibition can also explain the activity of FTIs in tumors with and without *ras* mutations. These proteins include Rho and others. Ras, Rho, and other proteins involved in oncogenesis also require geranylgeranylation for activation. This has led to the development of geranylgeranyl transferase inhibitors (GTIs). These GTIs, like FTIs, inhibit the growth of various cancer cell lines in vitro or in athymic mice[6].

The FTIs R115777 and SCH66336 have undergone the most clinical trials to date. Both agents are given orally. Clinical studies have shown that both R115777 and SCH66336 could inhibit farnesylation of HDJ2 proteins in peripheral blood mononuclear cells at doses below that causing dose-limiting toxicity.

Multiple studies have shown that colon cancers as well as lung cancers and premalignant colon tissues as well as lung tissues in both humans and mice have elevated levels of COX-2. The elevated levels of COX-2 play a critical role in the malignant pathways, and elevated COX-2 levels alone were sufficient to induce tumors in transgenic mice. In colon and lung cancer patients, those with elevated levels of COX-2 have been reported to have a worse prognosis than those with lower COX-2 levels in several studies.

These studies suggest that COX-2 is an excellent target for colon and lung cancer

therapy. This observation was supported by epidermiologic studies suggesting that chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) was associated with a reduced risk of colon and lung cancers. Subsequent studies showed that a variety of NSAIDs and specific COX-2 inhibitors could inhibit the growth of colon and lung cancer cells in vitro and in human colon and lung cancer xenografts in athymic mice. The combination of these COX-2 inhibitors with chemotherapeutic agents produced additive or synergistic growth inhibition[7, 8]. Inhibition of COX-2 produces effects other than just reductions in levels of VEGF and antiangiogenic effects.

COX-2 inhibitors such as celecoxib and rofecoxib are marketed for other indications but are now being tested in colon cancer chemoprevention trials and in colon and lung cancer therapy trials in combination with chemotherapeutic agents including capecitabine, paclitaxel and carboplatin.

Angiogenesis, or the formation of new blood vessels from preexisting vasculature, plays a major role in tumor growth and metastasis formation. Therefore, inhibiting tumor angiogenesis may be a promising therapeutic strategy.

The physiological control of angiogenesis involves a complex interplay between endogenous positive and negative regulators of blood vessel growth. Angiogenic growth factors comprise a family of 20 peptides that stimulate vascular proliferation through binding to specific endothelial cell receptors. In the healthy state, the angiogenic phenotype is governed by a precise balance between these stimulatory and inhibitory forces.

Numerous studies have shown that angiogenesis inhibition can suppress tumor growth in animals. Intervention with antiangiogenic agents early in tumorigenesis markedly diminishes both tumor burden and tumor size. Furthermore, these agents can be co-administered with cytotoxic chemotherapy or radiotherapy to achieve synergistic antitumor effects. As a rule, angiogenesis inhibition exerts a cytostatic effect, acting to stabilize disease rather than shrinking tumors. An important mediator involved in

angiogenesis is VEGF. The clinical importance of VEGF in tumor growth is supported by the fact that most tumors produce VEGF and that the inhibition of VEGF-induced angiogenesis significantly inhibits tumor growth in vivo. Increased VEGF expression has also been associated with metastasis of colorectal cancer. VEGF inhibitors under development are the recombinant human monoclonal antibody against VEGF and the small molecule VEGFR-tyrosine kinase inhibitor, SU5416 [9].

At the end of 2001, more than 60 antiangiogenic agents were in clinical trials, including endostatin and angiostatin. Phase I clinical trials of antiangiogenic agents have shown that these drugs, as a class, are better tolerated and possess fewer toxicities than conventional chemotherapy drugs. Phase II clinical trials have shown that disease stabilization or partial responses are common following antiangiogenic therapy. Such responses are consistent with cytostatic therapy. Definitive and efficacy studies of 12 antiangiogenic agents including Neovastat, Thalidomide and AG3340 (matrix metalloproteinases inhibitor) are being studied in phase III clinical trials.

Finally, a growing number of clinical trials are combining an antiangiogenic agent with standard cytotoxic drugs or radiation. Reducing tumor vascularity paradoxically increases drug delivery of chemotherapeutic agents, by decreasing the intratumoral interstitial pressure caused by leaky tumor vessels. Thus, combination therapies are anticipated to have synergistic antitumor effects.

While improved survival remains the ultimate endpoint for oncology trials, the identification, validation and standardization of surrogate markers for the antitumor effects of the above cytostatic agents are turn-key issues for optimizing the development of agents targeting novel molecular targets.

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