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Commentary
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Recent Molecular Immunological Chemotherapy for Gastrointestinal Malignancies

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Abstract

Efficacy of anticancer agents is generally dose-dependent and thus is determined by the Maximum Tolerated Dose (MTD) and Dose-Limiting Toxicities (DLT). Based on new theories such as the role of immune checkpoints in tumor cell survival, it seems important to investigate the optimum dosing method for antibody-drug conjugates that can have multimodal pharmacological actions, rather than inducing bone marrow suppression/immunosuppression at the MTD/DLT like traditional chemotherapy, allowing the cytotoxic anticancer agent to be administered at the Minimally Effective Cytotoxic Dose (MECD) that maintains host antitumor immunity together with cytotoxic activity. At present, both molecular-targeting agents and immune checkpoint inhibitors are available. As a future treatment strategy, we need to develop regimens that do not cause bone marrow suppression and do not require suspension or discontinuation of treatment due to toxicities. With such new regimens, cancer cells will be killed effectively while adverse reactions are reduced, so patients can enjoy improved high quality of life and longer progression-free survival. It is strongly anticipated that molecular-targeting therapy will be developed for gastrointestinal cancer, which will allow the total dose to be given safely at optimal schedules.

Keywords: Molecular-targeting therapy; Minimally effective cytotoxic dose (MECD); Maximum tolerated dose (MTD); Dose-limiting toxicities (DLT); Immunosuppression

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Commentary

In recent years, molecular-targeting therapy directed against tumor mutations has made dramatic advances. As a result, treatment of malignant melanoma, lung cancer, breast cancer, leukemia and lymphoma has undergone significant changes [1]. Many tumor-specific antibodies are now available, such as trastuzumab (an anti-HER2 humanized antibody) for breast cancer, rituximab (an anti-CD20 chimeric antibody) for B cell non-Hodgkin lymphoma, and mogamulizumab (an anti-CCR4 antibody) for adult T cell leukemia/lymphoma [1]. Furthermore, antibody-drug conjugates that combine antibodies with anticancer agents, such as gemutuzumabo zogamicin (anti-CD33 humanized antibody + calicheamicin) for acute myeloid leukemia (AML), trastuzumab emtansine (anti-HER2 antibody + tubulin polymerization inhibitor) for breast cancer, and brentuximab vedotin (anti-CD30 antibody + microtubule inhibitor) for CD30-positive Hodgkin lymphoma, have led to significant progress in pharmacological treatment strategies targeting specific tumors [1]. Moreover, immune checkpoint inhibitors have become available, such as nivolumab (an anti-PD-1/PD-L1 antibody) and ipilimumab (an anti-CTLA4 antibody), which are based on the new concept of suppressing immune checkpoints that prevent the immune system from attacking cancer cells. Some clinical studies have shown better results with these new agents than with conventional cytotoxic anticancer agents [2-5]. In addition to utilizing $CD4^+$ regulatory T cells (Treg) and myeloid-derived suppressor cells (MDSC), which are potent immune inhibitory cells, to avoid the host immune response, tumor cells inhibit the production/secretion of various cytokines such as interleukin-10 (IL-10), Transforming Growth Factor (TGF)-β, and Vascular Endothelial Growth Factor (VEGF). As a result, they become invisible to the host immune system. It is thought that unresponsive Cytotoxic T Lymphocytes (CTL) inhibit CTLA4 signaling and PD-1/PD-L1 signaling in the tumor environment, thus inducing potent anti-tumor immunity [6-10]. Molecular-targeting therapy has expanded the options for treatment and has extended the progression-free survival and overall survival of patients. Antibody drugs (high molecular weight agents) and low molecular weight chemical entities can be classified into 1) agents that target the molecular biological

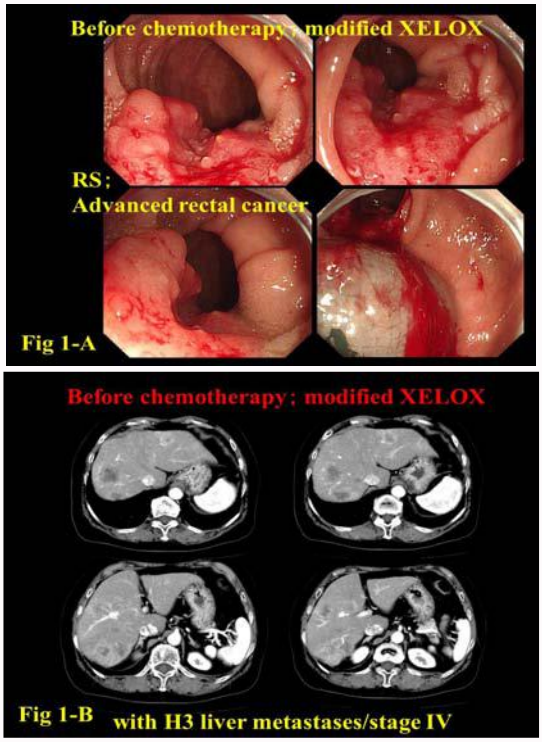

Figure 1: Colonoscopy findings and liver CT scans before and after chemotherapy are shown in Figure 1-A and 1-B, respectively.

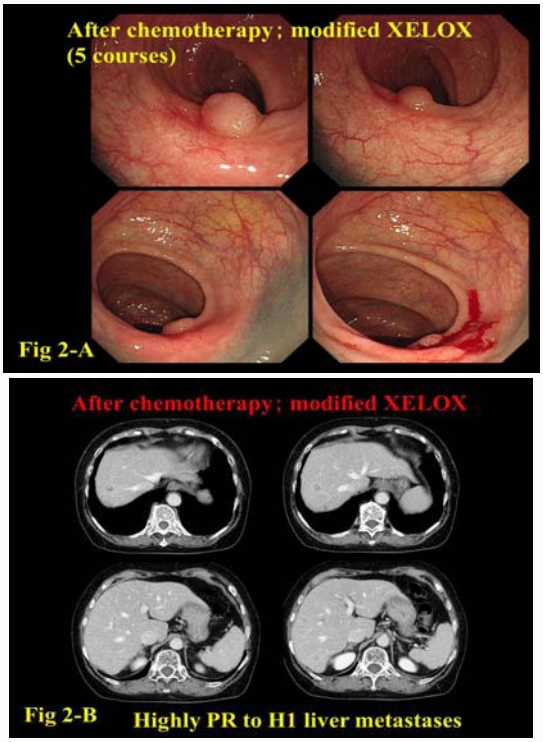

Figure 2: After treatment, the primary tumor almost disappeared (follow-up biopsy; cancer +) and H3 metastases improved to H1 (Figure 2-A, 2-B).

characteristics of cancer cells and 2) agents that act on the tumor microenvironment. The mechanisms of action of these new drugs are quite different from those of traditional cytotoxic chemotherapy agents. Mutations of oncogenes in cancer cells help to create a suitable environment for the survival and growth of these cells. Since cancer cells proliferate excessively, they are dependent on activation signals from these gene mutations, which has been calledoncogene addiction [11,12]. Many molecular-targeting agents are designed to preferentially kill cancer cells by blocking the activation of specific signaling pathways [13,14]. For example, three EGFR-TKI agents (gefinitib, erlotinib, and afanitib) are already available that target EGFR mutation-positive non-small cell lung cancer. When resistance develops to these agents due to T790M mutation, the third-generation agent osimertinib is now available. Moreover, two agents (crizotinib and alectinib) are available for ALK-translocated non-small cell lung cancer, while ceritinib can be used when tumors develop resistance to these treatments. However, there is concern that history may be repeated similar to the development of resistance to many antibiotics. In other words, the continuous development of new molecular-targeting agents for new cancer gene mutations may be needed. Unfortunately, development of a new drug is both hugely expensive and time-consuming, leading to a rapid increase of drug prices that has placed significant pressure on the health system in Japan and become an important social issue. The efficacy of cytotoxic anticancer agents, such as those inhibiting the growth of tumor cells and inducing apoptosis, is usually dose-dependent and thus is defined by the Maximum Tolerated Dose (MTD) and the Dose-Limiting Toxicities (DLT) [15-17]. Chemotherapy for hematological malignancies may be fundamentally different from that for solid tumors due to differences of cancer cell biology. To treat hematological malignancies such as leukemia, potent remission induction therapy is conducted according to the MTD/DLT with the aim of reducing the leukemic cell count to around 10^9 cells, followed by allogeneic hematopoietic stem cell transplantation. However, a novel theory of tumor immunity was recently proposed, which suggests that unlocking immune checkpoints protecting cancer cells in the tumor microenvironment will allow these cells to be recognized by the host immune system, leading to selective and efficient killing of tumor cells [2-5]. At present, trastuzumab has been approved for some patients with HER2-positive gastrointestinal cancer, specifically gastric cancer. In the case of colorectal cancer, tumor suppressor genes such as P53/APC/DCC and oncogenes such as K-ras/c-myc interact in a complex manner during a multi-step process of carcinogenesis, and treatment that can selectively block oncogenes (as is available for lung cancer) has not yet been identified. Accordingly, panitumumab and cetuximab cannot be used unless the most upstream RAS gene is maintained in colorectal cancer, while bevacizumab and ramucirumab do not require this precondition and are used relatively often in daily practice. However, appropriate dose selection for combination chemotherapy such as FOLFOX and FOLFIRI remains a challenge. Doses are selected based on the Phase 3 randomized trial, where the regimen was selected based on the MTD/DLT in Phase 1 and 2 studies performed in western countries. In Japan, a lower percentage of patients experience bone marrow suppression or suspension / discontinuation of therapy and there are more patients who can complete treatment. Accordingly, FOLFOX6 (oxaliplatin at 85mg/m^2) is often preferred. For the IRIS regimen that was developed in Japan, the dose of irinotecan was recently reduced from 125mg/m^2 to a range from 100mg/m^2 to 75mg/m^2 (25% reduction) [18,19]. Sensitivity to this drug is closely related to the level of expression of enzymes involved in its metabolism and degradation. Based on new theories such as the role of immune checkpoints in tumor cell survival, it seems important to investigate the optimum dosing method for antibody-drug conjugates that can

have multimodal pharmacological actions, rather than inducing bone marrow suppression/immunosuppression at the MTD/DLT like traditional chemotherapy, allowing the cytotoxic anticancer agent to be administered at the Minimally Effective Cytotoxic Dose (MECD) that maintains host antitumor immunity together with cytotoxic activity. Currently, both molecular-targeting agents and immune checkpoint inhibitors are available. As a future treatment strategy, we need to develop regimens that do not cause immunosuppression / bone marrow suppression and do not require suspension or discontinuation of treatment due to toxicities. With such new regimens, cancer cells will be killed effectively while adverse reactions are reduced, so patients can enjoy improved high Quality Of Life (QOL), high Quality-Adjusted Life Year (QALY) and longer progression-free survival. Also for colorectal cancer, new chemotherapy is being sought that allows the specified dose to be administered safety in a defined period.

Case presentation of chemotherapy using the Minimally Effective Cytotoxic Dose (MECD)

A 78-year-old woman with inoperable advanced rectal cancer (stage IV) underwent palliative chemotherapy for multiple liver metastases (H3). Her height, body weight, and body surface area were 159.0cm, 59.0kg, and 0.781m^2, respectively. Both the patient and her family members were elderly and only mild chemotherapy was desired. The primary tumor showed ulceration. She was treated with XELOX without the use of Avastin (bevacizumab). The dose of XELOX was reduced to approximately 50% of the recommended dose (second dose reduction step: oxaliplatinat 60mg/m^2). Five courses were administered [20,21]. Colonoscopy findings and liver CT scans before and after chemotherapy are shown in Figure 1-A and 1-B, respectively. After treatment, the primary tumor almost disappeared (follow-up biopsy; cancer +) and H3 metastases improved to H1 (Figure 2-A, 2-B). Although conversion surgery was recommended, the patient refused it. At present, her performance status is 0. In order to achieve complete remission of multiple lesions, an additional 5 courses of outpatient chemotherapy combined with Avastin are being conducted.

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