

# Investigational Drug Development for Solid Tumors

## Introduction

Investigational drug development for solid tumors is a representative research activity in the Division of Oncology/Hematology. In daily medical practice, patients with various cancers, including cancer of the breast, head and neck and malignant lymphomas, are treated with chemotherapy. These cancers are major and specific targets of the Division, and most patients with these malignancies have been treated by standard chemotherapy and/or in clinical trials. Primary unknown malignancy is another major target. Other various solid tumors, including gastrointestinal cancer, lung cancer, and soft tissue sarcoma, are treated mainly in early clinical trials of anticancer agents.

Our clinical and research activities are primarily focused on the following six fields:

1. Developmental therapeutics using new anticancer agents as phase I trials that are conducted by pharmaceutical companies.
2. Clinical pharmacology studies of commonly used drugs for adequate dose modification.
3. Development of combination chemotherapy involving a newly developed drug or new combination chemotherapy using already available drugs.
4. Disease-oriented clinical trials especially for breast, head and neck cancer, malignant lymphomas, and hematological malignancies.
5. High dose chemotherapy with peripheral blood stem cell support in experimental or standard treatment.
6. Standard treatment with chemotherapy in medical practice.
7. Palliative care research for terminal stage patients.

## Practice Activities

A variety of malignant diseases were treated in the past year. The major and specific target diseases of the Division were breast cancer, head and neck

cancer, and malignant lymphomas, and 218, 67, and 130 new patients, respectively, visited clinics of the Division in 2003. Corresponding number of patients who were treated in the hospital were, 101, 121 and 125 patients, respectively. These patients accounted for 70% of all patients admitted to the Division in 2003. Eligible patients were asked to participate in large phase II or III studies. Primary unknown cancers were other major targets of the Division, and 39 new patients visited our clinics in 2003. Gastrointestinal cancer including esophageal and colorectal cancer, lung cancer, pancreatic cancer, soft tissue sarcoma, and gynecological cancer, including uterine and ovarian cancer were also treated in the Division. For patients with diseases for which established standard chemotherapy is available but no phase II or III clinical trials are ongoing, standard chemotherapy was administered in routine medical practice. Patients who failed in standard chemotherapy or patients with cancer for which standard chemotherapy was not available were asked to participate in clinical studies of experimental therapy that is a major part of our research activities.

## Research Activities / Investigational Drug Development

### 1) Phase I study of novel drugs

Flavopiridol is a molecular targeting agent that inhibits cyclin-dependent kinases and modulates the cell cycle. Following a phase I study of flavopiridol infused over 24 hours every week, we have conducted the second phase I study of the drug using a different infusion schedule, a weekly 1-hour infusion.

Other new agents with molecular targets that we evaluated in phase I studies in 2003 included BAY-43-9006 (an inhibitor of raf kinases) and GW572016 (a new quinazolin derivative with an inhibitory activity on EGFR and ErbB2). Although the number of phase

I studies of molecular targeting drugs is increasing, a phase I study of a cytotoxic drug such as CHC12103 was also performed.

In contrast to these phase I studies that are at a very early stage of clinical development and that enroll patients with various cancers, phase I studies with a specific disease target are also underway. After we determined a recommended dose of fludarabine for patients with low grade lymphoma in a phase I study, we conducted a phase II study of the drug to evaluate the efficacy and safety of the drug. Also we have conducted a phase I study of 90Y-ibritumomab tiuxetan in patients with the same disease. For breast cancer, a phase I study of combination chemotherapy with capecitabine and docetaxel is now underway.

#### 2) Phase I study of new combination chemotherapy

A phase I study of combination chemotherapy with weekly administration of docetaxel and irinotecan was completed, and recommended combination doses and an optimal administration sequence of the drug combination have been determined. In addition, blood sampling for pharmacokinetic investigation has been performed in the study, and the pharmacokinetic drug-drug interaction and predictability of docetaxel clearance by hydrocortisone will be evaluated.

We have initiated a phase I study of combination chemotherapy of ranimustine, etoposide, cytarabine and melphalan with PBSCT support in patients with aggressive lymphomas, as well as a phase I study of concurrent chemoradiotherapy with cisplatin and S-1 in patients with locally advanced head and neck cancer. Pharmacokinetics of ranimustine and S-1 are also investigated in each study.

#### 3) Phase II/III study

Against breast cancer we have conducted two phase II studies using S-1 and furtulon. The study of furtulon was an investigator-driven study and pharmacokinetic evaluation was implemented to elucidate the difference in pharmacokinetics between furtulon and a related new drug, capecitabine. In a

randomized study we have evaluated the clinical relevance of the inhibitory activity of MS-209 on p-glycoprotein in patients with breast cancer treated with CAF chemotherapy. In this study, the influence of MS-209 on pharmacokinetics of doxorubicin, which is a concern as a p-glycoprotein inhibitor, is also being evaluated. We participated in a large international phase II/III study comparing exemestane and tamoxifen in patients with breast cancer. Patient accrual to the study has been completed. Another international study we are participating in is the HERA study which is a randomized study evaluating trastuzumab in adjuvant chemotherapy against HER2-positive breast cancer. Pharmacokinetics of trastuzumab given every 3 weeks is investigated in the study. Other large phase III studies we are participating in are JCOG studies for patients with breast cancer and malignant lymphoma and JALSG studies for patients with leukemia.

#### 4) Pharmacological studies

The investigational drugs that we are developing include not only anticancer agents but also supportive agents. We have performed a pharmacological study of S-8116 (oxycodone), a phase II study of epoetin beta (recombinant erythropoietin) and a pharmacological study of darbepoetin.

To develop better strategies for administration of anticancer agents, we are conducting population pharmacokinetic studies of anticancer agents that are commercially used in medical practice. Doxorubicin and docetaxel are currently evaluated in population pharmacokinetic studies. Another approach to improve cancer chemotherapy is a pharmacogenomics study. We pursue such an approach in cyclophosphamide as an in-house study as well as in irinotecan, taxanes, gemcitabine and S-1 as millennium projects.

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