

# 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 and lung cancers 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 cancers, 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. Research of supportive and palliative care for patients treated with chemotherapy or patients in the terminal stage.

## 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 270, 54, and 114 new patients, respectively, visited clinics of the Division in 2004. These patients accounted for 73% of the total of 594 patients visited our clinics in the

year. Corresponding number of patients who were treated in the hospital were, 125, 101 and 150 patients, respectively. These patients accounted for 79% of all patients admitted to the Division in 2004. Eligible patients were asked to participate in large phase II or III studies. Primary unknown cancers were other major targets of the Division, and 25 new patients visited our clinics in 2004. Gastrointestinal cancers including esophageal and colorectal cancers, lung cancer, pancreatic cancer, soft tissue sarcomas, genitourinary cancers, and gynecological cancers, including uterine and ovarian cancers 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. A patient with non-small cell lung cancer has been treated for more than 15 months without increase in her tumor size.

Other new agents with molecular targets that we evaluated in phase I studies in 2004 included BAY-43-9006 (an inhibitor of raf kinases) and GW572016 (a new quinazolin derivative with an inhibitory activity on EGFR and ErbB2). Although number of phase I studies of molecular targeting drugs is increasing, a phase I study of a cytotoxic drug such as RPR109881 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, clinical 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 are conducting a phase I/II study of bortezomib in patients with multiple myeloma

### 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 was determined. In addition, blood sampling for pharmacokinetic investigation was performed in the study, and the pharmacokinetic drug-drug interaction and predictability of docetaxel clearance by hydrocortisone are now analyzed.

To improve therapeutic efficacy of a standard treatment, a new experimental treatment should be developed. We have completed a phase I study of concurrent chemoradiotherapy with cisplatin and S-1 in patients with locally advanced head and neck cancer. We replaced 5-FU in the standard chemoradiotherapy with S-1 to improve the antitumor activity of the treatment, and a surprisingly high rate of complete response has been obtained in the phase I study. A phase II study is now planned as a multi-institutional study. In the phase I study, we investigated pharmacokinetics of S-1 given both orally and through a PEG tube to the stomach. No differences in pharmacokinetics were observed.

To develop a new regimen for patients with recurrent aggressive lymphomas, we are evaluating the efficacy and toxicity of a combination chemotherapy with methylprednisolone, etoposide and cytarabine. For patients with recurrent aggressive lymphomas that are chemo-sensitive, we are now conducting a phase I study of combination chemotherapy of ranimustine, etoposide, cytarabine and melphalan with PBSCT support to establish a standard conditioning regimen in Japan. Pharmacokinetics of ranimustine are also investigated.

A new combination chemotherapy of docetaxel and capecitabine is now under development as a pharmaceutical company-sponsored phase I study.

### 3) Phase II/III study

After finishing a phase I study of GW572013 (a

new quinazolin derivative with an inhibitory activity on EGFR and HER2) in our Division, a multicenter phase II study is now ongoing. We are evaluating the efficacy of the compound in patients with HER2-positive breast cancer who had been failed in trastuzumab treatment as well as in patients with HER2-negative breast cancer.

In a large international phase III study, we are evaluating trastuzumab in adjuvant chemotherapy against HER2-positive breast cancer. Pharmacokinetics of trastuzumab given every 3 weeks is investigated in the study. Another international study we are participating in is the HERA study which is a randomized 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. For patients with primary breast cancer, we are conducting a phase II study of primary chemotherapy followed by radiotherapy before surgical resections. A pathological complete response rate will be evaluated, and possibility of omitting surgical resection of a breast tumor will be sought in future.

### 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 darbepoetin and a phase III study of epoetin beta after we finished a phase II study.

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. In the study of docetaxel, concentrations of protein-unbound drug, which is considered to be pharmacologically active, are investigated. 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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