

Hematology & Oncology

Research Activities/Investigational Drug Development

1) Phase I studies of novel drugs

We are conducting phase I studies of newly developed anticancer agents in collaboration with pharmaceutical companies. These include both cytotoxic and molecular target drugs. We have completed the enrollment of patients in phase I studies of BAY-43-9006 (an inhibitor of raf and VEGFR kinases), RPR109881 (a new taxane), and ZK219477 (an epothilone derivative). We expect to finish our phase I studies of LY 317615 (a PKC inhibitor) and vinflunine (a vinca alkaloid) in a couple of months, and will continue to enroll patients to newly initiated phase I studies of LBQ707 (an oral camptothecin derivative), E7389 and ABI-007.

In contrast to these phase I studies that are at a very early stage of clinical development and that enroll patients with various different cancers, clinical studies on specific disease targets are also under way. After we determined the 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 its efficacy and safety. We have also conducted a phase I/II study of bortezomib in patients with multiple myeloma.

2) Phase I studies of new combination chemotherapy

To develop a new regimen for patients with recurrent aggressive lymphomas, we evaluated the efficacy and toxicity of a combination chemotherapy using methylprednisolone, etoposide and cytarabine. For patients with chemosensitive recurrent aggressive lymphomas, in order to establish a standard conditioning regimen in Japan, we are now

conducting a phase I study of chemotherapy with a combination of ranimustine, etoposide, cytarabine and melphalan with PBSCT support. The pharmacokinetics of ranimustine are also being 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 studies

We have participated in a multicenter phase II study of lapatinib (a new quinazoline derivative with inhibitory activity on EGFR and HER2) following completion of a phase I study. We evaluated the efficacy of the compound in patients with HER2-positive breast cancer who had failed trastuzumab treatment, as well as in patients with HER2-negative breast cancer. We are also evaluating the activity of gemcitabine and ixabepilone against breast cancer in multicenter phase II studies.

In a large international phase III study, we are evaluating trastuzumab in adjuvant chemotherapy against HER2-positive breast cancer. The pharmacokinetics of trastuzumab given every 3 weeks were investigated in this study. Another international study in which we are participating is a phase III trial of denosumab, evaluating its activity in preventing skeletal related events compared with zoledronate. We also contributed to a phase I study of denosumab in patients with breast cancer.

4) Pharmacological studies

To develop better strategies for the 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 being

evaluated in this way. In the docetaxel study, the concentration of free drug not bound to protein, which is the fraction considered to be pharmacologically active, is being investigated. Another approach to improve cancer chemotherapy is a pharmacogenomics study that we are pursuing with cyclophosphamide, as an in-house study as well as with irinotecan, taxanes, gemcitabine and S-1 as millennium projects. Certain genotypes are known to affect the activity of UGT1A1, which detoxifies SN-38, an active metabolite of irinotecan. We have found that *UGT1A1**6 causes alterations in the pharmacokinetics and toxicity of irinotecan to the same extent as *UGT1A1**28. Both of these genotypes should therefore be tested when UGT1A1 genotyping is performed before irinotecan is given to patients.

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