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Preface

For the last symposium of the millennium, the organizers and sponsor of the 16th Bristol-Myers Squibb Nagoya International Cancer Treatment Symposium decided to reflect on past achievements and anticipate new ones under the theme "Hematologic malignancies: pioneers in cancer therapy across the century from mustard to molecular targets and beyond." Once again, the symposium attracted more than 400 researchers and clinicians from around the world who heard 22 presentations detailing past, current, and future investigations into cancer treatment.

Emil J. Freireich (University of Texas M.D. Anderson Cancer Center, Houston) gave the keynote address at the 2000 Symposium, entitled "Can we conquer cancer in the 21st century?" His comprehensive review of progress in cancer treatment over the past 100 years ended on a note of optimism and set the stage for subsequent presentations in sessions covering oncogenicity and gene-targeting therapy and therapeutic strategies for further increases in cure rates.

The title of Session 1 was "Oncogenicity and gene-targeting therapy," during which seven researchers gave presentations. As reported by Minoru Yoshida and his group at the University of Tokyo, a group of derivatives of cyclic hydroxamic acid-containing peptides (CHAP) inhibit histone deacetylase (HDAC) at nanomolar concentrations. In particular, CHAP31 appears promising as a novel therapeutic agent in cancer treatment. In addition, the CHAP family may be useful in synthesis and high-throughput screening for new HDAC inhibitors.

Pier Paolo Pandolfi reviewed recent progress towards an understanding of the molecular mechanisms underlying acute promyelocytic leukemia (APL) and how this has led to therapeutic strategies using HDAC inhibitors and inorganic arsenicals. In particular, the role played by transcription of the retinoic acid receptor α (RARα) gene and its fusion products in the pathogenesis of APL was described in detail.

Target molecules in the treatment of leukemia have been the focus of work of Tomoki Naoe (Nagoya University School of Medicine, Japan) and his colleagues, in particular FLT3 tyrosine kinase. Until an FLT-specific inhibitor is developed, Dr Naoe noted that HSP90 inhibitors are promising in the treatment of acute myelocytic leukemia (AML) with mutant FLT3.

Leukemia has also been the focus of investigations by James D. Griffin (Dana Farber Cancer Institute, Boston). His presentation detailed biochemical analyses of the function of the oncoprotein BCR/ABL which is produced by the t(9;22) translocation associated with chronic myelogenous leukemia (CML). He concluded that PI3 K is important in the BCR/ABL transformation and that STI571 may be combined with other inhibitors of the PI3 K pathway to gain an additive effect.

Hisamaru Hirai and colleagues (University of Tokyo, Japan) have examined Evi-1 expression, since its transcriptional activation has been documented in myeloid malignancies. Evi-1, located on chromosome 3q26, represses transforming growth factor-β signaling by binding to Smad3, interacts with CtBP1 through its consensus motif, and inhibits Smad-induced transcription by recruiting a corepressor complex. These findings provide insight into potential therapeutic approaches, and indicate that specific HDAC inhibitors may be useful in the treatment of Evi-1-induced leukemias.

AML-1, one of the most frequently translocated genes in human leukemia, and the t(8;21), t(12;21) and inv(16) translocations, the ETS family transcription factor TEL, nuclear hormone corepressors, and the AML-1 cofactor CBFβ have been investigated by the group of Scott W. Hiebert (Vanderbilt University School of Medicine, Nashville). Their results suggest that HDAC inhibitors will be beneficial in leukemias associated with the t(8;21) and t(12;21) translocations and that other targets for therapy will be found with further exploration of the components of the corepression complexes bound by AML-1/ETO and TEL/AML-1.

Session 2 was entitled "Therapeutic strategies for further increase of cure rate." Thomas Büchner (University of Münster, Germany) reviewed dose-response effects in the treatment of systemic malignancies and

AML from the viewpoint of whether more chemotherapy is better or whether unacceptable toxicity occurs with further dose intensification. The conclusion was that while unlimited intensification therapy is not better, some improvements may be achieved in the treatment of patients with AML and other systemic cancers with further intensification.

In his presentation entitled "Acute myeloid leukemia in adults: where do we go from here?" Charles A. Schiffer (Wayne State University School of Medicine, Detroit) reviewed treatment trials in AML and suggested new directions that could be taken. Examples were the use of nonmyeloablative allogeneic stem cell transplantation (SCT) as a form of immunotherapy, refinements in autologous SCT, and manipulations of neoangiogenesis in the bone marrow, along with incorporation of newer agents such as monoclonal antibodies and the specific tyrosine kinase inhibitor STI571 into treatment regimens.

Alan K. Burnett (University of Wales College of Medicine, Cardiff, UK) examined allogeneic and autologous bone marrow transplantation (BMT) in AML. His review concluded that good-risk patients should not undergo transplantation unless they relapse, while poor-risk patients should receive transplantation as soon as identified in addition to additional antileukemic therapy. In standard-risk patients, transplantation may be effective early and may be more suitable than multiple courses of intensive chemotherapy. Dr Burnett recommended a definitive randomized clinical trial of transplantation since the results of chemotherapy continue to improve.

In a Japanese multicenter prospective trial, interferon α (IFNα) was compared with BMT in CML, and the results were reported by Kazunori Ohnishi (Hamamatsu University School of Medicine, Japan). In higher-risk patients, survival tended to be better in the related- and unrelated-donor BMT groups than in the IFNα group in younger patients, while the reverse tendency was seen in older patients. Therefore Dr Ohnishi recommended that prognostic factors such as age, Sokal risk score, and response to IFNα therapy be considered carefully before performing BMT in older patients. He also pointed that longer follow-up of the Japanese prospective trial patients is needed before any definitive conclusions can be reached.

The title of Session 3 was "New drugs and strategies from experience in hematologic malignancies to solid tumors." Norio Asou (Kumamoto University School of Medicine, Japan) reported the results of the Japan Adult Leukemia Study Group APL92 study, which was a multicenter study of differentiation with all-*trans*-retinoic acid (ATRA) alone or combined with chemotherapy, followed by intensive postremission chemotherapy in patients with APL. Prognostic factors were analyzed in an attempt to increase cure rates in the subsequent trial (APL97). Of 369 evaluable patients in APL92, 90% achieved a complete response (CR) with ATRA alone, 88% with ATRA plus later chemotherapy, and 89% with ATRA plus initial and later chemotherapy. Favorable prognostic factors for achieving CR included younger age, no or mild purpura, high serum total protein levels, low lactate dehydrogenase levels, and no or mild disseminated intravascular coagulation. In the ongoing APL97 study, an intensified chemotherapy study group was included for patients with leukocyte counts $\geq 3.0 \times 10^9$/l.

A review of arsenic compounds as anticancer agents was given by Zhen-yi Wang (Shanghai Institute of Hematology, RoC). He noted that newly diagnosed and relapsed patients with APL achieved high CR rates of 85–93% in clinical trials using arsenic trioxide and that arsenic at high concentrations induces apoptosis in numerous cancer cell lines in vitro. Dr Wang concluded that arsenic compounds are effective in the treatment of APL and that their activity in other types of cancer should be investigated further.

The therapeutic activity of the Abl-specific tyrosine kinase inhibitor STI571 was reviewed by Brian Druker (Oregon Health Sciences University, Portland). Preclinical and phase I clinical studies have demonstrated that STI571 is a new therapeutic agent for the treatment of CML. Dose-response relationships with Bcr-Abl tyrosine kinase inhibition and mechanisms of relapse in blast crisis are being analyzed in ongoing trials.

Shimon Slavin (Hadassah University Hospital, Israel) described the adoptive allogeneic cell therapy with donor lymphocyte infusion for nonmyeloablative stem cell transplantation (NST) that his group has been using since 1987 in patients who relapse following BMT. Their results show that NST is relatively safe in patients with high-risk disease and effective in hematologic malignancies and nonmalignant indications for BMT. It may thus permit early, safer application of therapy involving allogeneic SCT combined with innovative immunotherapy with allogeneic donor lymphocytes.

Because the majority of indolent B cell non-Hodgkin lymphoma (B-NHL) patients cannot be cured with current chemotherapy regimens, the group of Kensei Tobinai (National Cancer Center Hospital, Tokyo, Japan) have investigated the chimeric monoclonal antibody rituximab in Japanese B-NHL patients. The results of their phase I and II trials were similar to those achieved in the USA with this agent, although the pharmacokinetic data varied more widely between the Japanese patients and the $T_{1/2}$ was slightly longer. Two multicenter phase II studies in Japan with rituximab stopped enrolling patients in 2000 and the results are awaited. Based on the results from previous trials, the agent is effective in the treatment of relapsed indolent B-NHL and mantle cell lymphoma, with acceptable toxicity.

Relapsed B-NHL was also the focus of the presentation by Thomas E. Witzig (Mayo Clinic, Rochester, Minnesota) who reviewed trials with yttrium-90-conjugated ibritumomab tiuxetan. Although further study is required to determine the optimal point in the disease course when this modality should be used, yttrium-

90-ibritumomab tiuxetan radioimmunotherapy appears useful in patients with B-NHL.

Kazunari Taira (University of Tokyo, Japan) reported on behalf of his group the results of research on the cytoplasmic localization and transport of ribozymes in mammalian cells. Since ribozymes selectively bind and cleave specific target RNAs, they are potentially useful tools to suppress the expression of cancer-causing genes. Dr Taira's group has confirmed that transcripts must be localized in the cytoplasm to maintain the activity of ribozymes in cells and that cytoplasmic ribozymes appear significantly more active than nuclear ribozymes.

The final presentation, by Nagahiro Saijo (National Cancer Center Hospital, Tokyo, Japan) summarized the new strategies that will likely be important in anticancer therapy in the 21st century, which include nontoxic target-based therapies, monoclonal antibodies, and tyrosine kinase inhibitors. He also introduced the Japanese genome project called the Millennium Project begun in 2000. Under the project, Dr Saijo's group will work on "identification of genomic polymorphisms related to pharmacokinetics/pharmacodynamics and their clinical applications" in the hope of discovering new molecular targets for chemotherapy and developing individually tailored therapies for patients with cancer.

We would like to express our gratitude to all the participants in the 16th Bristol-Myers Squibb Nagoya International Cancer Treatment Symposium. Continuing international cooperation among researchers and clinicians in oncology will contribute to a better understanding of the mechanisms of carcinogenesis and the development of more effective anticancer therapies. We also thank Bristol-Myers Squibb for continuing generous support for this symposium series.