Cancer Chemother Pharmacol (2004) 54 (Suppl 1): S1–S3
DOI 10.1007/s00280-004-0879-x

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Preface

Published online: 21 August 2004

The 19th Bristol-Myers Squibb Nagoya International Cancer Treatment Symposium focused on the diagnosis, management and prevention of gastric, colorectal, intestinal, pancreatic and liver cancers under the theme of "State of the Arts for Digestive Organs". This topic was first discussed at the first Nagoya Symposium in 1985. Since then, considerable progress has been made in the field. Over 400 physicians and scientists from around the world attended the 2003 Symposium to listen to presentations on the current status and future perspectives of cancers of the digestive organs, and to participate in "Meet the Expert" sessions.

John S. Macdonald (St. Vincent's Comprehensive Cancer Center, New York) began the meeting with the keynote address entitled "Clinical overview: adjuvant therapy of gastrointestinal cancer". He evaluated the current status of adjuvant and neoadjuvant therapies for gastric cancer and speculated on approaches that will be used in the future. Dr. Macdonald also reviewed the use of adjuvant chemotherapy in the management of resected large bowel cancers and pancreatic cancers.

The title of the first session was "Gastric Cancer". *Helicobacter pylori* infection has a causal relationship to gastritis, gastric atrophy, gastric cancer and MALT lymphoma in the stomach. A summary of the clinical studies and experiments in animal models demonstrating this relationship was given by Toshiro Sugiyama (Hokkaido University Graduate School of Medicine, Japan). In vitro experimental studies have shown that virulence factors of *H. pylori* interact with gastric epithelial cell signaling related to carcinogenesis. These in vivo and in vitro studies may result in a new strategy for the effective prevention of the development of gastric cancer induced by *H. pylori* infection.

Two topics were addressed by Masaki Mori (Kyushu University, Japan) in his presentation. First he discussed the development of a scoring system using cDNA microarray to estimate prognosis in gastric cancer patients more comprehensively. This technique has been associated with several practical problems, such as sample preparation. The second topic focused on the use of laser microdissection and cDNA microarray analysis to identify genes related to metastasis and histologic differentiation of gastric cancer. Dr. Mori also reviewed the advantages and disadvantages of cDNA microarray analysis in the context of gastric cancer.

Junichi Sakamoto (Kyoto University Graduate School of Medicine, Japan) talked about Japanese and global perspectives of adjuvant chemotherapy for gastric cancer, and outlined the prevailing differences in terms of its use and outcome. Dr. Sakamoto reviewed data from clinical trials comparing Western and Japanese lymphadenectomy operations. He also described the development of adjuvant chemotherapy for gastric cancer in Japan from the 1960s to the 1980s, and findings from adjuvant chemotherapy trials restarted in the late 1980s.

The second session was entitled "Colorectal and Intestinal Cancer". Heinz-Josef Lenz (University of Southern California, Los Angeles) talked about two of the most promising new targets in the treatment of colorectal cancer: the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF). Agents that inhibit the EGFR (cetuximab) or bind to VEGF (bevacizumab) have demonstrated clinical activity as single agents and in combination with chemotherapy in phase II and phase III clinical trials. Dr. Lenz summarized the findings of these trials and concluded that the goal in the future will be to predict which specific chemotherapy and targeted agent combination will most benefit individual patients.

Yoshiro Niitsu (Sapporo Medical University School of Medicine, Japan) looked at chemopreventive strategies for colorectal cancer. Dr. Niitsu and colleagues have

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succeeded in identifying human aberrant crypt foci (ACF) in situ using magnifying endoscopy. This research has led to a randomized, double-blind, chemopreventive trial targeting ACF. Studies on overexpression of glutathione S-transferase P1-1 as a target molecule in human colon carcinogenesis have resulted in the synthesis of a GSTP1-1-specific inhibitor. Current studies are focusing on the chemopreventive effect of this inhibitor agent in colorectal carcinogenesis in the rat.

The use of imatinib mesylate for the treatment of gastrointestinal stromal tumors (GISTs) was the focus of the presentation by Akira Sawaki (Aichi Cancer Center Hospital, Japan). Imatinib mesylate has rapidly become the first-line treatment for patients with unresectable GIST. However, as Dr. Sawaki pointed out, there are a number of problems associated with the use of imatinib mesylate in patients with GIST. Resolution of these problems, from current ongoing clinical trials and associated laboratory studies, could lead to the development of more effective therapies against GISTs.

Richard M. Peek (Vanderbilt University School of Medicine, Nashville) reviewed the developments in the treatment of colorectal cancer by NSAIDs via COX-2 inhibition. Studies have shown that COX-2 is involved in tumor development and progression. Dr. Peek discussed the potential mechanisms by which COX-2 mediates its tumorigenic effects. Findings from recent specific COX-2 inhibitor studies indicate that a widely used and relatively safe class of drugs will represent a viable and effective means of preventing colorectal cancer—a disease with few treatment options which results in over a half-million deaths per year.

The theme of colorectal cancer was continued in the next presentation given by Richard M. Goldberg (University of North Carolina at Chapel Hill). New combination chemotherapy regimens and the integration of novel targeted therapies with cytotoxic chemotherapies are areas of active clinical investigation. He summarized findings of selected phase III studies that have tested these new chemotherapy options and led to new standards of care and better expectations for patients with advanced colorectal cancer. Fluorouracil, oral fluoropyrimidines, raltitrexed, irinotecan, oxaliplatin and their combinations, which have all been tested in the management of colorectal cancer, were described. Dr. Goldberg concluded that while current chemotherapy practices are primarily defined by cytotoxic therapies, the integration of targeted therapies is imminent and holds the promise of further improving outcomes for patients with colorectal cancer.

Christoph Lengauer (Johns Hopkins University School of Medicine, Baltimore) delivered the Basic Lecture on ''CIN-ful cancers''. Findings from his group suggest that aneuploidy in cancers is the result of chromosomal instability (CIN)—a process in which dividing cells segregate their chromosomes with decreased fidelity. Dr. Lengauer explained the definition of chromosomal instability, reviewed evidence for its causal role in tumor development, and proposed possible mechanisms behind initiation of chromosomal instability in cancer cells.

''Pancreatic Cancer'' was the title of the third session. Henry Q. Xiong (University of Texas MD Anderson Cancer Center, Houston) began this session by talking about molecular targeting therapy for pancreatic cancer. The recent elucidation of the roles of cyclooxygenase and lipoxygenase has led to several distinct therapeutic advances. Many novel agents have been developed and are undergoing clinical investigations, such as monoclonal antibodies against EGFR, tyrosine kinase inhibitors (TKIs), farnesyl transferase inhibitors (FTIs), Bay43-9006, CI-1040, CCI-779, celecoxib, and LY293111. Dr. Xiong outlined advances in the development of these agents. He concluded that while several of these agents have shown promising activity in the preclinical setting, clinical data to date has so far been unimpressive. The results of several planned and ongoing randomized trials are eagerly awaited.

Takuji Okusaka (National Cancer Center Hospital, Japan) focused on new approaches for chemotherapy in patients in Japan with advanced pancreatic cancer. Pancreatic cancer is the fifth leading cause of cancer-related mortality in Japan, with an estimated annual incidence of approximately 20,000 cases. Dr. Okusaka described the use of 5-FU and gemcitabine, and summarized data from clinical trials of new agents irinotecan and NK911 for pancreatic cancer patients in Japan. He also outlined a novel arterial infusion chemotherapy for advanced pancreatic cancer and two other treatment approaches: non-myeloablative allogeneic stem cell transplantation and gene therapy. The evolving understanding of molecular and genetic biology should facilitate research to develop novel target-based agents and to establish individualized therapy regimens for this disease.

The theme of the closing session was ''Hepatocellular Carcinoma'', and began with a talk by Masashi Mizokami (Nagoya City University Graduate School of Medical Sciences, Japan). Dr. Mizokami hypothesized that a longer duration of the HCV endemic accounts for the differing HCC burden between the USA and Japan. His group has looked at long-term serial serum samples containing hepatitis C virus (HCV) from the USA and Japan which were molecularly clocked to determine the time-origin of the HCV epidemic. Based on his group's findings and data from other studies, he predicted that an increase in HCC prevalence will occur in the US over the next two to three decades.

Alan P. Venook (University of California, San Francisco) talked about key research issues in the management of HCC. He suggested that one reason for the slow progress in finding newer biological therapies for the treatment of HCC was that HCC is almost always two diseases in one: underlying liver disease and cancer. This makes clinical trial design more cumbersome and

increases the risks of participating in clinical trials for HCC. Dr. Venook listed some of the major challenges to advancing the management of HCC, and described possible solutions and those new treatments which are more likely to have an impact on HCC.

We would like to express our gratitude to all the participants in the 19th Bristol-Myers Squibb Nagoya International Cancer Treatment Symposium. We also thank Bristol-Myers Squibb for their continuing generous support for this symposium series.