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## Combination Chemotherapy, Hyperthermia Helpful in Pancreatic, Neuroendocrine Cancer

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July 17, 2003 — The combination of cisplatin (CIS), gemcitabine (GEM), interferon-alpha (IFN-alpha), granulocyte-macrophage colony-stimulating factor (GM-CSF), and fever-range, long-duration whole-body hyperthermia (FR-WBH) is safe, well tolerated, and offers clinical benefit to patients with pancreatic cancer or neuroendocrine neoplasia, according to a presentation on July 14 at the 94th annual meeting of the American Association for Cancer Research (AACR) held in Washington, D.C.

"The exciting implication of our phase I study is that FR-WBH increases the clinical effectiveness of optimally combined CIS, GEM and metronomic, low-dose IFN-alpha," lead author Joan Marie C. Bull, MD, from the University of Texas Medical School in Houston, told Medscape.

Using an in vivo model and preclinical data, the investigators designed a phase I protocol combining optimally timed and sequenced CIS, GEM, low-dose metronomic IFN-alpha, and GM-CSF with FR-WBH using the Heckel 2001 radiant heat device.

The protocol consisted of an escalating dose of CIS (50 to 100 mg/m<sup>2</sup>) on day 1; fixed dose daily subcutaneous IFN-alpha (100,000 IU) from day 1 to protocol completion; FR-WBH (40.0°C for six hours) with simultaneous GEM (600 mg/m<sup>2</sup> over 60 min) on day 3; GEM (600 mg/m<sup>2</sup> over 60 min) on day 10; and GM-CSF (250 mg/m<sup>2</sup>/day) from day 14 through day 24. Treatment cycles were repeated at day 28. Fentanyl, lorazepam, and phenergan were used for light conscious sedation.

Of 24 patients with advanced or metastatic cancer treated between November 1999 and October 2002, 22 (91.6%) had been previously treated with up to five chemotherapy regimens. Median age was 55 years (range, 25-78 years); there were 10 women and 14 men. Race distribution was 20 white patients, three African-Americans, and one Hispanic. Zubrod performance scores were 1 to 3.

Median number of treatment cycles was four (range, 1-9), and the time to reach target core temperature was 60 to 140 minutes. The maximally tolerated dose was determined by dose-limiting toxicity, defined as World Health Organization grade III hematological or extra-hematological toxicity. Two of three patients had grade III thrombocytopenia at 70 mg/m<sup>2</sup> CIS; one of three developed grade II thrombocytopenia after three cycles of CIS 70 mg/m<sup>2</sup>; and three patients experienced grade 1 leukopenia at CIS 70 mg/m<sup>2</sup>. Other adverse events linked to CIS at 70 mg/m<sup>2</sup> were one grade III ototoxicity, and grade II neuropathy in two of three patients. The investigators therefore estimated the maximally tolerated dose of CIS to be 60 mg/m<sup>2</sup> and recommended that dose for phase II trials.

Of 17 objective responses (OR), nine (38%) were partial responses (PRs), including two that were greater than 90%. Five patients (21%) had ORs lasting more than five months. Clinically meaningful PRs occurred in five of seven patients with pancreatic cancer, and in all three with neuroendocrine cancers.

"The toxicity was minimal and the responses quite high with the phase I trial, suggesting that we advance to the phase II trial for patients with inoperable or metastatic pancreatic cancer," Dr. Bull said. "We are also writing a phase II trial for neuroendocrine tumors, and for stage III and IV lung cancer."

Third party payors paid for the standard chemotherapy, and the National Cancer Institute–funded Clinical Research Center covered the cost of the investigational fever-range whole-body hyperthermia. None of the authors report any pertinent financial disclosures.

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*Reviewed by Gary D. Vogin, MD*

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