Summary

Although striking evidence exists that argues for the usefulness of hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of peritoneal carcinomatosis (PC), many aspects of this therapy have yet to be standardized. As interest in this modality increases, there are several avenues of research to be explored. How important is the cytocidal effort, the temperature elevation increment, and the length of time for the hyperthermic perfusion? We review what is known and what may be explored in the near future.

Key Words: Hyperthermic intraperitoneal chemotherapy; future directions; IP delivery methods.

1. THERAPEUTIC AGENTS

Most of the current studies published on HIPEC use cisplatin or mitomycin C as the agents infused during surgery. Although there are compelling data about the effectiveness of both these compounds, recent studies have looked at other agents that may be useful in HIPEC. By exploring different agents, or combinations of agents, we hope to find alternatives for patients that present with platinum-refractory disease and to decrease the side effects noted with cisplatin and mitomycin C.

2. CARBOPLATIN

Carboplatin is an analog of cisplatin, which has been shown in multiple studies to have less nonhematologic toxicity. Although myelosuppression continues as a main toxicity, carboplatin has been shown to decrease nephrotoxicity, neurotoxicity, and emetogenesis compared with cisplatin (1). Initial
traditional intravenous studies compared cisplatin and carboplatin in suboptimally debulked ovarian cancers and suggested that there was equivalent activity between these two compounds (1,2). In 2003, Ozols published the results of Gynecologic Oncology Group (GOG) 158, which was a large multicenter trial for optimally resected stage III ovarian cancer patients. This noninferiority study concluded that carboplatin plus paclitaxel was as effective in the treatment of optimally resected ovarian cancer as the previous standard of care, cisplatin/paclitaxel (3). Based on this study, as well as two European studies, carboplatin/paclitaxel became the standard of therapy for ovarian cancer in the United States. Because of the superior toxicity profile, ease of use, and reduced toxicity, most infusion centers had switched to outpatient carboplatin infusion for ovarian cancer in the mid-1990s.

The use of HIPEC with carboplatin has been used little in published studies, especially in comparison to cisplatin. Cisplatin and carboplatin have been compared in the presence of hyperthermia in a rat tumor model. Intratumor platinum concentrations were notably higher in the cisplatin rat models at 37°C and 41°C compared with carboplatin, but both were shown to have increased cytotoxicity with the increase in temperature (4). Additionally, hematologic toxicity of carboplatin and cisplatin were similar when combined with hyperthermia in another rat tumor model (5). To date, there is a dearth of published studies in patients with carcinomatosis comparing carboplatin and cisplatin. A phase I study by Steller (see Chapter 10) evaluated the feasibility, toxicity, and pharmacokinetics of carboplatin administered by HIPEC in small-volume ovarian cancer patients (6). Six patients underwent optimal cytoreductive procedures as initial treatment for stage II/III epithelial ovarian cancer (EOC). During a 90-min perfusion, carboplatin infusions were performed at 41°C–43°C. There was wide variability of the dose absorbed into the systemic circulation, ranging from 27%–77%, but 5 of the 6 patients absorbed >50% of the drug dose systemically. Systemic toxicities, particularly myelosuppression, were significant, which is an indirect reflection of substantial systemic absorption. Based on this data, it would appear carboplatin is not an ideal choice for IP therapy because of the high rate of systemic exposure and resulting toxicities, but head-to-head comparisons with cisplatin have not been reported.

3. TAXANES

Since the publication of GOG 111 in 1996, normothermic intravenous paclitaxel with a platinum agent has been the standard of care for the front-line treatment of ovarian carcinoma, with response rates of between 60% and 80% (7). Two studies have looked at paclitaxel and thermal enhancement. Rietbroek showed that paclitaxel exposed to two different murine tumor cell lines at 41°C and 43°C showed no enhancement of cytotoxicity when compared to a