HIPEC treatment of peritoneal carcinomatosis in colorectal and gastric cancer
Braam, Hidde

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CHAPTER 9

Selection of chemotherapy for hyperthermic intraperitoneal use in gastric cancer

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Abstract

Background
Several studies have shown the potential benefit of cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC) in gastric cancer patients. At present the most effective chemotherapeutic regime in HIPEC for gastric cancer is unknown. The aim of this review was to provide a comprehensive overview of chemotherapeutic agents used for HIPEC in gastric cancer.

Methods
A literature search was conducted using the PubMed database to identify studies on chemotherapy used for HIPEC in gastric cancer patients.

Results and conclusion
The chemotherapeutic regime of choice in HIPEC for gastric cancer has yet to be determined. The wide variety in studies and study parameters, such as chemotherapeutic agents, dosage, patient characteristics, temperature of perfusate, duration of perfusion, carrier solutions, intraperitoneal pressure and open or closed perfusion techniques, warrant more experimental and clinical studies to determine the optimal treatment schedule. A combination of drugs probably results in a more effective treatment.
Background

Worldwide, approximately one million patients are diagnosed with gastric cancer every year. With a five-year survival rate of 15–25%, gastric cancer is the second leading cause of cancer-related death. The disease is often diagnosed at an advanced stage and frequently with synchronous peritoneal metastasis. Locoregional recurrence and peritoneal carcinomatosis are the most frequently encountered sites of treatment failure after potentially curative resection. The survival of patients with peritoneal dissemination of gastric cancer is poor, with a median survival of 3.1 months.

Following the beneficial outcome in various other peritoneal surface malignancies (e.g., pseudomyxoma, colorectal, ovarian), cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is increasingly investigated as a treatment option in selected gastric cancer patients. The indications for HIPEC in gastric cancer are roughly divided in HIPEC as a prophylaxis following curative surgery to prevent peritoneal metastasis and local recurrence, or as a treatment of established peritoneal carcinomatosis. In advanced gastric cancer patients, a recent meta-analysis of ten randomized controlled trials has shown that prophylactic HIPEC may potentially improve overall survival and may prevent local recurrence.

One randomized controlled trial has reported the outcome of HIPEC in patients with established peritoneal carcinomatosis of gastric cancer. A significant median survival benefit was shown in the CRS + HIPEC group (11.0 versus 6.5 months, \( P = 0.046 \)) compared to CRS alone, whereas the rate of serious adverse events did not differ significantly.

The characteristics of the ideal drug for intraperitoneal usage are extensive. For instance, important attributes are proven systemic activity, favorable pharmacokinetics, concentration related cytotoxicity, adequate tissue penetration, acceptable local toxicity, synergy with hyperthermia and safety of administration for hospital personnel. Various chemotherapeutic agents are used in HIPEC for gastric cancer patients, among which mitomycin, cisplatin and taxanes, but the most effective drug or combination of drugs has yet to be determined. The aim of this review is to provide a comprehensive overview of present chemotherapeutic agents used for HIPEC in gastric cancer.
Methods

A literature search was conducted using the PubMed database to identify studies, published between January 1980 and June 2013, on chemotherapy used for HIPEC in gastric cancer patients. The following search terms, in various combinations, were used: intraperitoneal, peritoneal, gastric, stomach, neoplasms, cancer, pharmacokinetics, mitomycin, platinum compounds, taxanes, anthracyclines, irinotecan, catumaxomab, hyperthermia, intraoperative period, time to progression, survival, response rate. Relevant citations were separately analyzed.

Results are presented for each individual chemotherapeutic drug. Data are presented according to the in vivo or in vitro effect on gastric cancer. For each drug, studies on intraperitoneal use in humans or animals are described; when extensive data of intraperitoneal administration of the drug in humans were present, animal studies were not further analyzed. Studies on the intraperitoneal administration were analyzed for toxicity profiles, pharmacokinetics and effect status. Studies on the subject of environmental hazards and safety of drug administration are presented in summary. For each category of drugs a summary is provided of its present status and role in intraperitoneal administration in gastric cancer patients. In the pharmacokinetic analysis, attention was focused on area under the curve (AUC) ratio, which is calculated by dividing the total perfusate concentration over time by the total plasma concentration over time, which gives a representation of the amount of chemotherapy absorbed during the HIPEC procedure. Additionally, the maximum concentration of chemotherapy (Cmax) in the perfusate and plasma with corresponding ratio is reported. Furthermore, intraperitoneal half-life of the drug is an important pharmacokinetic parameter, which is influenced by the uptake of chemotherapy through the peritoneum and degradation of the agent during intraperitoneal perfusion. A high AUC ratio may reflect high local efficacy and low systemic toxicity. Consequently, a high AUC ratio demonstrates the pharmacokinetic advantage of administrating chemotherapeutic drugs intraperitoneal compared to intravenous administration of the same chemotherapeutic drugs.

Several questions currently exist in the execution of HIPEC perfusion in gastric cancer patients. HIPEC is generally performed with an open abdominal approach using a coliseum technique or closed abdominal technique which uses transabdominal drains to deliver and remove the intraperitoneal chemotherapy during HIPEC. Centers treating peritoneal surface malignancies use different temperatures during intraoperative
intraperitoneal perfusion, frequently hyperthermia between 41 and 43 °C is applied, resulting from the in vitro heat augmentation of several drugs used for intraperitoneal administration. However, normothermic perfusion is currently also investigated, as the evidence for additional benefit of hyperthermia is limited. The duration of perfusion is a matter of investigation, frequently a 90 min HIPEC is performed, based on the first studies describing intraoperative intraperitoneal chemotherapy. However, experiments with both shorter and longer perfusion have been performed in various HIPEC regimes. Lastly, an important question is whether monotherapy or a combination of drugs should be used. Studies investigating the influence of the aforementioned variances in HIPEC treatment were presented when appropriate. Using clinicaltrials.gov, currently performed trials of intraperitoneal administration of chemotherapeutic drugs in gastric cancer patients were identified and directions of future research are indicated.

### Results

**Mitomycin**

Following the widespread use of mitomycin in HIPEC for colorectal peritoneal carcinomatosis (PC) and pseudomyxoma peritonei, nearly all studies on HIPEC in gastric cancer have used mitomycin as shown in Table 1. Mitomycin acts as an alkylating agent and produces DNA cross-linking, thus inhibiting DNA and RNA synthesis. The response rate of systemic mitomycin in gastric cancer is moderate and inferior to newer drugs, such as taxanes and platinum-containing drugs. Furthermore, the safety profile of systemic mitomycin is problematic.

In the largest pharmacokinetic analysis of intraperitoneal mitomycin in 145 patients, the AUC ratio was 27, which is consistent with several other studies. Mitomycin was administered in a single dose of 15 mg/m² and perfusion was continued for 90 min at 42 °C. The peak plasma concentration was 0.25 μg/mL at 30 min, compared to the peak intraperitoneal concentration of 10 μg/mL at the start of the perfusion. After 90 min, 29% of the total dose was still in the perfusion fluid and 9% was excreted in the urine. Thus, 62% of the drug was retained within the patient’s body.
Table 1. Hyperthermic intraperitoneal chemotherapy studies in gastric cancer (series with ≥10 patients)

<table>
<thead>
<tr>
<th>Author, year</th>
<th>N</th>
<th>Drug</th>
<th>Dosage</th>
<th>Duration (min)</th>
<th>Temp. (°C)</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koga, 1988</td>
<td>91</td>
<td>MMC</td>
<td>8–10 mg/L in 8–12 L</td>
<td>50–60</td>
<td>40–45</td>
<td>Prophylactic</td>
</tr>
<tr>
<td>Hamazoe, 1994</td>
<td>42</td>
<td>MMC</td>
<td>10 mg/L in 10–12 L</td>
<td>50–60</td>
<td>40–45</td>
<td>Prophylactic</td>
</tr>
<tr>
<td>Ikeguchi, 1995</td>
<td>78</td>
<td>MMC</td>
<td>80–100 mg/m²</td>
<td>50–60</td>
<td>40–45</td>
<td>Prophylactic</td>
</tr>
<tr>
<td>Fujimoto, 1999</td>
<td>71</td>
<td>MMC</td>
<td>10 mg/L in 3–4 L</td>
<td>120</td>
<td>43–45</td>
<td>Prophylactic</td>
</tr>
<tr>
<td>Beaujard, 2000</td>
<td>42</td>
<td>MMC</td>
<td>10 mg/L in 4–6 L</td>
<td>90</td>
<td>46–49</td>
<td>PC</td>
</tr>
<tr>
<td>Yonemura, 2001</td>
<td>48</td>
<td>MMC</td>
<td>30 mg in 8–10 L</td>
<td>60</td>
<td>42–43.5</td>
<td>Prophylactic</td>
</tr>
<tr>
<td>Kim, 2001</td>
<td>52</td>
<td>MMC</td>
<td>10 mg/L</td>
<td>120</td>
<td>42–44</td>
<td>Prophylactic</td>
</tr>
<tr>
<td>Hall, 2004</td>
<td>34</td>
<td>MMC</td>
<td>40 mg in ± 3 L</td>
<td>120</td>
<td>38.5–41</td>
<td>PC</td>
</tr>
<tr>
<td>Shen, 2009</td>
<td>43</td>
<td>MMC</td>
<td>10 mg/L + 10 mg at 60 min</td>
<td>120</td>
<td>40–42.5</td>
<td>PC</td>
</tr>
<tr>
<td>Costa, 2012</td>
<td>10</td>
<td>MMC</td>
<td>34 mg/m²</td>
<td>90</td>
<td>40–42</td>
<td>Prophylactic</td>
</tr>
<tr>
<td>Fujimura, 1994</td>
<td>22</td>
<td>MMC + CDDP</td>
<td>30 mg/kg + 300 mg/kg</td>
<td>60</td>
<td>41–42</td>
<td>Prophylactic</td>
</tr>
<tr>
<td>Yonemura, 1995</td>
<td>79</td>
<td>MMC + CDDP</td>
<td>30 mg + 300 mg</td>
<td>60</td>
<td>41.5–43.5</td>
<td>Prophylactic</td>
</tr>
<tr>
<td>Rovelli, 2006</td>
<td>12</td>
<td>MMC + CDDP</td>
<td>25 mg/m² + 100 mg/m²</td>
<td>60</td>
<td>41–43</td>
<td>PC</td>
</tr>
<tr>
<td>Zhu, 2006</td>
<td>118</td>
<td>MMC + CDDP</td>
<td>5 mg/L + 50 mg/L in 5–6 L</td>
<td>60</td>
<td>42–44</td>
<td>Both</td>
</tr>
<tr>
<td>Scaringi, 2008</td>
<td>37</td>
<td>MMC + CDDP</td>
<td>6 L of MMC 120 mg + 6 L of CDDP 200 mg/m²</td>
<td>60–90</td>
<td>41–43</td>
<td>Both</td>
</tr>
<tr>
<td>Li, 2010</td>
<td>54</td>
<td>MMC + CDDP</td>
<td>5 mg/L in 5–6 L + 50 mg/L</td>
<td>60</td>
<td>42–44</td>
<td>Both</td>
</tr>
<tr>
<td>Yang, 2011</td>
<td>34</td>
<td>MMC + CDDP</td>
<td>30 mg + 120 mg in 6 L</td>
<td>60–90</td>
<td>43</td>
<td>PC</td>
</tr>
<tr>
<td>Königsrainer, 2012</td>
<td>11</td>
<td>MMC + CDDP</td>
<td>25–35 mg/m² + 50 mg/m²</td>
<td>90</td>
<td>42</td>
<td>PC</td>
</tr>
<tr>
<td>Mizumoto, 2012</td>
<td>16</td>
<td>MMC + CDDP</td>
<td>20 mg + 100 mg</td>
<td>60</td>
<td>41–42</td>
<td>PC</td>
</tr>
<tr>
<td>Hirose, 1999</td>
<td>32</td>
<td>MMC + CDDP + ETP</td>
<td>20 mg + 100 mg + 100 mg</td>
<td>50</td>
<td>41–44.5</td>
<td>Both</td>
</tr>
<tr>
<td>Fujimura, 2000</td>
<td>15</td>
<td>MMC + CDDP + ETP</td>
<td>25 mg/L + 10 mg/L + 20 mg/L</td>
<td>60</td>
<td>42</td>
<td>PC</td>
</tr>
<tr>
<td>Kunisaki, 2002</td>
<td>45</td>
<td>MMC + CDDP + ETP</td>
<td>15 mg + 150 mg + 150 mg in 5–6 L</td>
<td>40</td>
<td>42–43</td>
<td>Prophylactic</td>
</tr>
<tr>
<td>Author, year</td>
<td>N</td>
<td>Drug</td>
<td>Dosage</td>
<td>Duration (min)</td>
<td>Temp. (°C)</td>
<td>Setting</td>
</tr>
<tr>
<td>-------------</td>
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<td>-------------------------------------------</td>
<td>----------------</td>
<td>------------</td>
<td>---------</td>
</tr>
<tr>
<td>Yonemura, 2005&lt;sup&gt;104&lt;/sup&gt;</td>
<td>107</td>
<td>MMC + CDDP + ETP</td>
<td>30 mg + 300 mg + 150 mg</td>
<td>60</td>
<td>42–43</td>
<td>PC</td>
</tr>
<tr>
<td>Kunisaki, 2006&lt;sup&gt;105&lt;/sup&gt;</td>
<td>73</td>
<td>MMC + CDDP + ETP</td>
<td>30 mg + 300 mg + 300 mg in 5–6 L</td>
<td>40</td>
<td>42–43</td>
<td>PC</td>
</tr>
<tr>
<td>Glehen, 2010&lt;sup&gt;127&lt;/sup&gt;</td>
<td>159</td>
<td>MMC ± CDDP</td>
<td>30–50 mg/m² ± 50–100 mg/m²</td>
<td>60–120</td>
<td>41–42.5</td>
<td>PC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L-OHP ± CPT11</td>
<td>360–460 mg/m² ± 100–200 mg/m²</td>
<td>30</td>
<td>43</td>
<td>PC</td>
</tr>
<tr>
<td>Zhao, 2012&lt;sup&gt;146&lt;/sup&gt;</td>
<td>26</td>
<td>CDDP + 5-FU</td>
<td>40 mg/m² + 0.75 mg/m²</td>
<td>120</td>
<td>41–41.8</td>
<td>PC</td>
</tr>
<tr>
<td>Wu, 2012&lt;sup&gt;13&lt;/sup&gt;</td>
<td>32</td>
<td>L-OHP</td>
<td>460 mg/m² in 3–4 L</td>
<td>60</td>
<td>42.5–43.5</td>
<td>PC</td>
</tr>
</tbody>
</table>

MMC mitomycin C, CDDP cisplatin, L-OHP oxaliplatin, ETP etoposide, CPT11 irinotecan, 5-FU 5-fluorouracil, PC peritoneal carcinomatosis, *duration of intraperitoneal perfusion.
The toxicity profile of intraperitoneal mitomycin has been described extensively and has shown acceptable morbidity and limited systemic toxicity. In vitro, heat augmentation of mitomycin has been established in multiple, including gastric, cell lines. Mitomycin can be safely used in HIPEC as the environmental exposure demonstrated by ambient air and biological monitoring, is below the detection limit of 1 μg/L. Mitomycin is a safe drug for HIPEC in gastric cancer patients, but, resulting from its relative limited systemic effect in gastric cancer patients, other drugs should be investigated.

Platinum-based agents
The platinum-containing drugs cisplatin and oxaliplatin are both frequently used antineoplastic drugs in gastrointestinal malignancies and have been extensively investigated. After intracellular hydrolysis, the reactive products of these drugs bind irreversibly to DNA which results in inhibition of DNA synthesis. As shown in Table 1, cisplatin has frequently been studied in HIPEC for gastric cancer, almost invariably in combination with mitomycin. The dosage of cisplatin in this studies varied between 50 and 200 mg/m² with perfusion times ranging from 60 to 90 min. Oxaliplatin has been investigated in only one study, including 32 patients treated with 460 mg/m² oxaliplatin for 60 min at 43 °C. In this retrospective case series, the median survival increased from 10.4 months with CRS to 15.5 months in CRS + HIPEC, and no differences were observed in serious adverse events between CRS or CRS + HIPEC.

In an in vitro study, five gastric cancer cell lines were found to be more sensitive to oxaliplatin compared to cisplatin. In the systemic treatment of advanced gastric cancer a small but significant survival benefit of oxaliplatin over cisplatin was observed in a meta-analysis, while intravenous oxaliplatin was associated with less toxicity and better tolerability. There are no randomized studies comparing these two drugs in gastric cancer patients. In a rat model comparing intraperitoneal administration of cisplatin and oxaliplatin, the peritoneal and plasma AUC were both higher for oxaliplatin. Although, this did not result in significant differences in platinum concentrations in tissues such as kidney, lung, liver, intestines and peritoneal tumors. These data suggest pharmacological advantages of oxaliplatin compared to cisplatin, but these were not enough to induce significant response differences.

The standard dosage of oxaliplatin for intraperitoneal use, 460 mg/m² for 30 min, is based on a phase I trial performed by Elias et al. in colorectal cancer. As 5-FU and oxaliplatin have a proven synergistic activity, induction systemic administration of 5-fluorouracil (5-
FU) and leucovorin is often added prior or during the HIPEC-procedure to enhance the cytotoxic effect of oxaliplatin. An overview of the pharmacokinetic analyses in humans of intraoperative intraperitoneal cisplatin or oxaliplatin is depicted in Table 2 and Table 3. The AUC ratios vary between 2.9 and 20.6 for cisplatin and between 12.8 and 13.7 for oxaliplatin. The results of pharmacokinetic studies vary widely based on the various sampling schedules and other parameters, including patient characteristics, dosage, temperature of perfusate, duration of perfusion, type of carrier solution, intraperitoneal pressure, and the HIPEC technique (open versus closed), which makes the comparison between studies difficult. The maximal concentration (Cmax) in the perfusate in HIPEC was consistently higher than the plasma Cmax for both cisplatin and oxaliplatin, resulting in Cmax ratios between 10 and 36 and between 19 and 32 for cisplatin and oxaliplatin, respectively. After 30 min of perfusion with oxaliplatin, approximately half of the oxaliplatin is located in the perfusion fluid and discarded. Thus, half of the oxaliplatin remains in the body, however, the exact location and activity of the agent is unknown. After 90 min of perfusion with cisplatin, approximately 75% is absorbed in the body. These results lead to a $T_{1/2}$ in the perfusate of about 30 min for oxaliplatin and 45 min for cisplatin.

In animal models, high pressure administration of cisplatin and oxaliplatin both resulted in increased tissue penetration. The safety and efficacy, including tissue penetration, of high pressure administration of cisplatin and oxaliplatin have not been investigated in humans.

The toxicity of both cisplatin and oxaliplatin is acceptable, with limited hematological adverse effects, but in contrast to oxaliplatin, cisplatin is nephrotoxic. Systemic administration of sodium thiosulfate diminishes the risk of development of renal toxicity. Howell et al. have demonstrated that sodium thiosulfate diffuses into the peritoneal cavity after intravenous administration. The concentrations were ten times lower than in the systemic compartment and were found, based on in vitro data, not high enough to inhibit the intraperitoneal anti-tumor activity of cisplatin.
Table 2, Pharmacokinetic analysis of intraoperative intraperitoneal cisplatin

<table>
<thead>
<tr>
<th>Author, year</th>
<th>N</th>
<th>Dosage (mg/m²)</th>
<th>Carrier solution</th>
<th>Duration (min)</th>
<th>Temp. (°C)</th>
<th>Absorbed (%)</th>
<th>T₁/₂ perfusate (min)</th>
<th>AUC ratio</th>
<th>Cmax ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stephens, 1996¹⁸</td>
<td>8</td>
<td>50</td>
<td>PD fluid</td>
<td>120</td>
<td>41–43</td>
<td>86 ± 6</td>
<td>48 ± 14</td>
<td>6.9 ± 3.6</td>
<td>15 ± 1</td>
</tr>
<tr>
<td>van de Vaart, 1998¹⁹</td>
<td>5</td>
<td>50–70</td>
<td>Isotonic saline</td>
<td>90</td>
<td>42</td>
<td>76</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cho, 1999²⁰</td>
<td>56</td>
<td>100–400</td>
<td>Isotonic saline</td>
<td>90</td>
<td>42–43</td>
<td>73 ± 20</td>
<td></td>
<td>12.9 ± 17.5</td>
<td>10</td>
</tr>
<tr>
<td>Kern, 2002²¹</td>
<td>5</td>
<td>150</td>
<td>Ringer's solution</td>
<td>60</td>
<td>43.5</td>
<td>28.8 ± 6</td>
<td>3.1¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Panteix, 2002²²</td>
<td>16</td>
<td>60–100 mg</td>
<td>Isotonic saline</td>
<td>90</td>
<td>41–43</td>
<td>65 ± 13</td>
<td>57.6</td>
<td>7.3 ± 4.3</td>
<td></td>
</tr>
<tr>
<td>Rossi, 2002²³</td>
<td>4</td>
<td>31–44ᵇ</td>
<td>Isotonic saline or PD fluid</td>
<td>90</td>
<td>42</td>
<td>76 ± 7</td>
<td>20.6 ± 6.0</td>
<td>36 ± 5</td>
<td></td>
</tr>
<tr>
<td>Royer, 2005²⁴</td>
<td>11</td>
<td>50</td>
<td>Isotonic saline</td>
<td>120</td>
<td>37</td>
<td>43.8</td>
<td></td>
<td>2.9 ± 1.6</td>
<td>5.9</td>
</tr>
<tr>
<td>Cotte, 2011²⁵</td>
<td>40</td>
<td>0.8–1.5ᶜ</td>
<td>PD fluid</td>
<td>90</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cashin, 2012²⁶</td>
<td>10</td>
<td>50</td>
<td>PD fluid</td>
<td>90</td>
<td>41–43</td>
<td>67 ± 10</td>
<td>18.4</td>
<td>6.3 ± 1.5</td>
<td>19</td>
</tr>
<tr>
<td>Median (range)</td>
<td>55</td>
<td>50–400</td>
<td>(50–400)</td>
<td>90</td>
<td>42</td>
<td>74.5</td>
<td>43.8</td>
<td>6.6 ± 1.5</td>
<td>17</td>
</tr>
</tbody>
</table>

AUC ratio AUC in perfusion divided by the AUC in the plasma, Cmax ratio maximum concentration of perfusate divided by the maximum plasma concentration. ¹Calculated from data. ᵇmg/L. ᶜmg/kg.
### Table 3, Pharmacokinetic analysis of intraoperative intraperitoneal oxaliplatin

<table>
<thead>
<tr>
<th>Author, year</th>
<th>$N$</th>
<th>Dosage (mg/m$^2$)</th>
<th>Carrier solution</th>
<th>Duration (min)</th>
<th>Temp. (°C)</th>
<th>Absorbed (%)</th>
<th>$T_{1/2}$ perfusate (min)</th>
<th>AUC ratio</th>
<th>Cmax ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elias, 2002$^{17}$</td>
<td>20</td>
<td>260–460</td>
<td>5% dextrose</td>
<td>30–40</td>
<td>42–44</td>
<td>50</td>
<td>40</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Elias, 2002$^{17}$</td>
<td>14</td>
<td>460</td>
<td>5% dextrose$^a$</td>
<td>30</td>
<td>42–44</td>
<td>54–60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stewart, 2008$^{28}$</td>
<td>12</td>
<td>200</td>
<td>5% dextrose</td>
<td>120</td>
<td>40–42.5</td>
<td>70 ± 24</td>
<td>13.7 ± 4.7</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Mahteme, 2008$^{29}$</td>
<td>8</td>
<td>427</td>
<td>5% dextrose</td>
<td>30</td>
<td>41.5–43</td>
<td>48 ± 7.6</td>
<td>29.5 (21–41)</td>
<td>12.8 ± 2.9</td>
<td>28</td>
</tr>
<tr>
<td>Ferron, 2008$^{30}$</td>
<td>24</td>
<td>360–460</td>
<td>5% dextrose</td>
<td>30</td>
<td>42–43</td>
<td>40–68</td>
<td>29.4 (18–42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valenzuela, 2011$^{31}$</td>
<td>30</td>
<td>360</td>
<td>4% icodextrin</td>
<td>40 (30–60)</td>
<td>42–43</td>
<td>132</td>
<td>13.2</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Perez, 2012$^{32}$</td>
<td>36</td>
<td>364.5</td>
<td>4% icodextrin</td>
<td>30–60</td>
<td>42–43</td>
<td>76.8</td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perez, 2012$^{32}$</td>
<td>13</td>
<td>399.5</td>
<td>5% dextrose</td>
<td>30–60</td>
<td>42–43</td>
<td>71.4</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>382 (200–460)</td>
<td></td>
<td></td>
<td>37.5 (30–120)</td>
<td>42.5 (40–44)</td>
<td>52 (40–68)</td>
<td>70 (18–132)</td>
<td>13.2 (12.8–13.7)</td>
<td>29.5 (19–33)</td>
</tr>
</tbody>
</table>

$^a$Osmolarity of solution varying between 100 and 300, AUC ratio AUC in perfusion divided by the AUC in the plasma, Cmax ratio maximum concentration of perfusate divided by the maximum plasma concentration.
Mortality after CRS + HIPEC seems equal for cisplatin and oxaliplatin, and varies between 0% and 7.6%. In a matched-pair analysis, no significant differences in toxicity were found between the use of oxaliplatin versus mitomycin plus doxorubicin. Additionally, in a retrospective analysis of 187 patients, hematological toxicity rates did not differ between patients undergoing HIPEC with oxaliplatin or mitomycin in colorectal cancer. Most drugs for intraperitoneal perfusion are administered in chloride-containing solutions. Because of its degradation in sodium-based solutions, oxaliplatin is preferably dissolved in dextrose 5%, which may cause pronounced electrolyte disturbances, including hyperglycaemia. As this degradation is limited, and does not affect in vitro cytotoxicity, further research is warranted to investigate whether oxaliplatin for HIPEC can be dissolved in other solutions with similar clinical efficacy and safety.

In vitro, hypotonic carrier solutions were shown to increase the uptake of platinum-drugs and to increase the cytotoxicity of cisplatin. In humans, hypotonic solutions did not result in clinically relevant improved pharmacokinetics or tissue penetration, although increased hemorrhage and thrombocytopenia have been described after hypotonic administration of oxaliplatin. An enhanced effect of hyperthermia has been demonstrated for both oxaliplatin and cisplatin. In a murine model, hyperthermic oxaliplatin resulted in higher peritoneal concentrations and lower plasma concentrations compared to normothermic oxaliplatin. Furthermore, hyperthermia resulted in increased tissue penetration of oxaliplatin. In cisplatin the effect of hyperthermia on its pharmacokinetics is unsettled. In one study, a four-fold increase in tissue concentration after hyperthermia has been demonstrated, yet these results could not be confirmed in another study.

Although multiple studies have incorporated a platinum-based antineoplastic drug in HIPEC, the exact role of cisplatin and oxaliplatin in HIPEC for gastric cancer remains to be elucidated. Currently, there appears to be a slight favor for the use of oxaliplatin as its efficacy appears to be higher and serious electrolyte disturbances can be avoided with perfusion times limited to 30 min.

### Taxanes
The taxane alkaloids, paclitaxel and docetaxel, are widely used in the treatment of various cancers including gastric, ovarian, and breast cancer. The anticancer activity of taxanes is based on the stabilization of microtubule formation causing arrest in the G2M phase of the cell cycle. The systemic administration of docetaxel based therapy in the palliative setting in gastric cancer patients has shown better response rates compared to non-taxane
Chemotherapy selection for HIPEC in gastric cancer

based chemotherapy. Paclitaxel and docetaxel are barely soluble in various solvents and are therefore dissolved as micellar preparations. Paclitaxel is dissolved in Cremophor EL and ethanol, whereas docetaxel is dissolved in Polysorbate-80. Preclinical data suggests that docetaxel is more suitable than paclitaxel for intraperitoneal administration since the cell permeability of paclitaxel is significantly inhibited by its solvent, resulting in a decreased tumor- and cell penetration for paclitaxel compared to docetaxel.

Several animal and human studies have shown favorable pharmacokinetics of intraperitoneally administered taxanes. In animal models, AUC-ratios of docetaxel and paclitaxel as high as 153 to 976 have been described. Drug concentrations of docetaxel in tissues in contact with perfusion fluid were higher than control tissues outside the abdominal cavity demonstrating adequate tissue penetration. Intraperitoneal injection of docetaxel was shown to result in an increased survival in mice with peritoneal metastases of gastric cancer. Tang et al. investigated the safety and efficacy of CRS + HIPEC with docetaxel and carboplatin using a rabbit model with PC of gastric cancer. A survival benefit was observed in the CRS + HIPEC group versus controls but differentiation between the effect of carboplatin and docetaxel was not possible.

In Asia, several catheter-based-intraperitoneal studies in humans have shown acceptable safety of intraperitoneal taxanes, and confirm the favorable pharmacokinetics of intraperitoneally administered taxanes. In humans, hyperthermic intraperitoneal taxanes have mainly been studied in ovarian malignancies; Table 4 gives an overview of the studies with intraoperative intraperitoneal taxanes. These studies show acceptable safety of taxanes in CRS + HIPEC.

To our knowledge, De Bree et al. have conducted the only study using hyperthermic intraperitoneal docetaxel in humans in patients with gynecological malignancies using a dosage of 75 mg/m² docetaxel at 41–43 °C. Death occurred in two elderly patients with a high volume intraperitoneal tumor load, probably reflecting poor patient selection (mortality rate 10%). Docetaxel-induced hematological toxicity was limited. The peak intraperitoneal versus plasma concentration ratio ranged between 17 and 95 (average 45), while the AUC ratio varied between 105 and 555 (average 207).
<table>
<thead>
<tr>
<th>Author, year</th>
<th>N</th>
<th>Primary tumour</th>
<th>Drug(s)</th>
<th>Dosage (mg/m²)</th>
<th>Duration (min)</th>
<th>Temp. (°C)</th>
<th>Absorbed (%)</th>
<th>AUC ratio</th>
<th>Cmax ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rufian, 2006</td>
<td>33</td>
<td>Ovarian</td>
<td>Paclitaxel</td>
<td>60</td>
<td>60</td>
<td>41–43</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bae, 2007</td>
<td>22</td>
<td>Ovarian</td>
<td>Paclitaxel</td>
<td>175</td>
<td>90</td>
<td>43–44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Bree, 2008</td>
<td>13</td>
<td>Ovarian</td>
<td>Paclitaxel</td>
<td>175</td>
<td>120</td>
<td>41–43</td>
<td>78 (59–89)</td>
<td>387 ± 260</td>
<td>1178 ± 817</td>
</tr>
<tr>
<td>Munoz-Casares, 2009</td>
<td>14</td>
<td>Ovarian</td>
<td>Paclitaxel</td>
<td>60</td>
<td>60</td>
<td>41–43</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim, 2010</td>
<td>18</td>
<td>Ovarian</td>
<td>Paclitaxel</td>
<td>175</td>
<td>90</td>
<td>43–44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Munoz-Casares, 2011</td>
<td>10</td>
<td>Ovarian</td>
<td>Paclitaxel</td>
<td>60</td>
<td>60</td>
<td>41–43</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ansaloni, 2012</td>
<td>11</td>
<td>Ovarian</td>
<td>Paclitaxel + cisplatin</td>
<td>175 + 100</td>
<td>90</td>
<td>41.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Bree, 2003</td>
<td>20</td>
<td>Ovarian</td>
<td>Docetaxel</td>
<td>75</td>
<td>120</td>
<td>41–43</td>
<td>79.5 (62–92)</td>
<td>207 (105–555)</td>
<td>45 (17–95)</td>
</tr>
</tbody>
</table>
The ideal dosage of intraperitoneal taxanes is not known. Catheter-based studies have shown that administration of docetaxel at 100 mg/m² every 3 weeks is tolerable. The same holds true for 60 mg/m² weekly. To date, there are no studies performed to determine the maximum tolerated dose of taxanes during intraoperative intraperitoneal administration. In CRS + HIPEC, the perfusion fluid containing the chemotherapeutic agent is cleared at the end of the procedure and the systemic uptake thereafter will largely be reduced, whereas in catheter-based intraperitoneal chemotherapy the agent remains active until it is completely cleared from the body. Heat stability of paclitaxel and docetaxel has been demonstrated up to 43 °C. Several experiments have studied the combination of hyperthermia and taxanes in vitro and in vivo with conflicting results. For paclitaxel, thermal enhancement has been found in vitro at 43 °C. However, other studies showed no thermal enhancement or even decreased cytotoxicity of paclitaxel. For docetaxel similar conflicting results have been reported.

**Anthracyclines**

The antibiotic antineoplastic anthracyclines, epirubicin and doxorubicin, bind to DNA, inhibit DNA and RNA synthesis, and inhibit DNA repair through topoisomerase II inhibition. In systemic gastric cancer treatment, epirubicin is frequently used in triple-therapy with fluorouracil and cisplatin or oxaliplatin, although the benefit of adding anthracyclines is uncertain. Doxorubicin is the most frequently studied anthracycline in intraperitoneal chemotherapy. Pharmacokinetic analyses of intraperitoneal doxorubicin has shown favorable pharmacokinetics, with peritoneal to plasma AUC ratios of 73–78, 128 for tumor tissue to plasma, and 1.8 tumor tissue to peritoneal fluid. After 90 minutes of perfusion, 88–93% of the applied doxorubicin was cleared from the peritoneal cavity. Hyperthermia moderately augments the cytotoxicity of doxorubicin in vitro. In an animal model, pharmacokinetics were not influenced by hyperthermia, but it did increase tissue concentrations of doxorubicin in the small bowel, omentum and spleen. Intraperitoneal doxorubicin (15 mg/m²), typically together with cisplatin, has been used for peritoneal sarcomatosis, peritoneal mesothelioma, and appendiceal malignancies. In higher doses (30 mg/L) doxorubicin causes local toxicity by extensive peritoneal inflammation leading to fibrosis and obstruction, while in lower doses (15 mg/m²), sclerosis formation is limited and does not compromise gastrointestinal function. Cardiotoxicity, which is frequently dose-limiting in systemic administration, has not been described after intraperitoneal administration of doxorubicin. Although anthracyclines are used in the
systemic treatment of gastric cancer, there are no published studies to date on intra-peritoneal administration for gastric cancer.

5-Fluorouracil

After activation, 5-fluorouracil (5-FU) inhibits thymidylate synthase, thereby depleting thymidine triphosphate which is a necessary component of DNA synthesis. Additionally, 5-FU is incorporated into RNA to replace uracil and inhibit cell growth. 5-FU, intravenously or its oral prodrug capecitabine, is an important drug in many (neo)adjuvant and palliative chemotherapeutic regimes for gastrointestinal cancers including gastric cancer. Although the AUC ratio of intraperitoneal 5-FU is over 400, it does not seem to be an appropriate drug for hyperthermic intraperitoneal chemotherapy for several reasons: first, in a mixed solution 5-FU is not compatible with various other chemotherapeutic drugs. Its cycle specificity favors multiple administrations, thus 5-FU has mainly been used as an early postoperative intraperitoneal drug. 5-FU is only to a limited extent augmented by hyperthermia. Finally, oral administration is relatively safe with limited toxicity. In 2006, a consensus meeting of experts in the treatment of peritoneal surface malignancy has concluded that 5-FU is not a good candidate for hyperthermic intraperitoneal chemotherapy.

As described earlier, 5-FU is used systemically in combination with oxaliplatin as bidirectional chemotherapy in CRS + HIPEC. Van der Speeten et al. described the pharmacokinetics of intraoperative intravenous 5-FU. Interestingly, after 20 min the concentration of intraperitoneal 5-FU exceeded the plasma concentration and stayed higher throughout the rest of the 90 min of intraperitoneal perfusion. This resulted in a peritoneal to plasma AUC ratio of 2.3. The authors explain this phenomenon by the fact that 5-FU quickly distributes to all the compartments, including the intraperitoneal perfusion fluid, but the hepatic metabolism of 5-FU rapidly decreases the plasma concentration of 5-FU, while the intraperitoneal concentration stays at a relatively constant level, with limited diffusion back into the central compartment. The clinical benefit of this bidirectional administration of chemotherapy has not yet been established. Future studies should elucidate more of the pharmacokinetics, especially the tissue distribution, of systemic perioperative 5-FU.
Chemotherapy selection for HIPEC in gastric cancer

Irinotecan

Irinotecan (CPT-11) is a pro-drug which has cytotoxic effects when converted by carboxylesterase to SN-38. SN-38 binds reversibly to the topoisomerase I-DNA complex preventing religation of the cleaved DNA strand. In a meta-analysis systemic administration of irinotecan in advanced and metastatic gastric cancer was associated with a non-significant trend towards better survival. In experimental setting, hyperthermia enhanced cytotoxicity of irinotecan. The activation of irinotecan occurs mainly in the liver, making it theoretically an unfavorable drug for intraperitoneal administration. However, the drug has been investigated in several animal and human intraperitoneal studies, showing intraperitoneal conversion of CPT-11 to SN-38. Although the conversion rate was lower after intraperitoneal administration compared to intravenous administration, the exposure of peritoneum to SN-38 was higher. The AUC ratio of SN-38 varied between 3.7 and 14.8 depending on the concentration of administered CPT-11. The efficacy of intraperitoneal irinotecan has been demonstrated in several animal studies. In the largest study in humans no statistically significant difference was noted in survival after CRS + HIPEC using oxaliplatin with or without irinotecan in 146 colorectal patients with established PC, which may reflect the inefficacy of irinotecan as an intraperitoneal drug.

Etoposide

Etoposide is an anticancer drug, which induces DNA breakage and inhibition of topoisomerase II enzyme. Systemically, etoposide has been investigated in various combinations including cisplatin, doxorubicin, 5-FU, and leucovorin. Although an early report on the usage of etoposide, cisplatin and doxorubicin showed promising results in advanced gastric cancer patients, subsequent studies could not confirm the favorable results of this combination. So far, no other studies could demonstrate a significant beneficial effect of etoposide in adjuvant or palliative setting in systemic gastric cancer treatment. Additionally, increased rates of toxicity have been reported in regimes using etoposide.

Nearly all studies of intraperitoneal etoposide are catheter-based and performed in patients with ovarian carcinoma. Pharmacokinetic analysis showed favorable pharmacokinetics with an AUC-ratio of 47. Intraoperative administration of etoposide in combination with cisplatin and or mitomycin has been performed in gastric cancer patients, with acceptable toxicity. However, some studies report significant toxicity.
and morbidity associated with intraperitoneal administration of etoposide.\textsuperscript{106,107} There is limited data on the supplementary value of hyperthermic intraoperative intraperitoneal etoposide. In vitro, there is controversy regarding the enhancement of cytotoxicity using hyperthermia.\textsuperscript{108-110} In conclusion, resulting from the low systemic potential of etoposide and frequent toxicity, other chemotherapeutics seems more suitable for intraperitoneal intraoperative usage in gastric cancer patients.

**Catumaxomab**

In 2009, catumaxomab was registered for the treatment of malignant ascites of various EpCAM-positive malignancies, including ovarian, gastric, breast and colorectal cancer. Catumaxomab is a monoclonal, trifunctional antibody, which binds to EpCAM-positive cells, and then activates the immune system resulting in killing of the tumor cell. Between 85 and 100\% of gastric cancer cells express EpCAM.\textsuperscript{111} In a recent study, all 35 tissue samples of peritoneal metastasis of gastric cancer overexpressed EpCAM.\textsuperscript{112} EpCAM is also expressed on normal epithelial cells but not in mesothelial tissue. In other tissues, EpCAM is only expressed basolaterally and is shielded by tight junctions. In contrast, tumor cells express EpCAM, accessible for binding, on the entire cell surface.\textsuperscript{113} Thus, the only cells expressing EpCAM in the peritoneal cavity are tumor cells, making the intraperitoneal route promising for the administration of catumaxomab.

In a randomized controlled trial, patients with malignant ascites of gastric cancer were treated with paracentesis alone or paracentesis and four 6-hour intraperitoneal infusions of catumaxomab at doses of 10, 20, 50 and 150 $\mu$g on days 0, 3, 7 and 10, respectively.\textsuperscript{114} Intraperitoneal infusions of catumaxomab significantly increased the paracentesis-free survival (15 versus 44 days, $P < 0.0001$) and increased the overall survival (median, 44 versus 71 days, $P = 0.03$). This study demonstrated high efficacy of intraperitoneal catumaxomab for malignant ascites. Treatment related serious adverse events occurred in 15\% of the patients and consisted mainly of abdominal pain and cytokine release–related symptoms (pyrexia, nausea, and vomiting). No treatment related mortality was reported. Additionally, 83\% of the patients received all four infusions, reflecting acceptable tolerability.

Despite these promising results, it is uncertain whether catumaxomab, with or without hyperthermia, is suitable for intraoperative perfusion in gastric cancer patients. In patients with advanced gastric cancer (T2b-T4, N+/−, M0), one randomized phase 2 trial has been
conducted using intraoperative intraperitoneal catumaxomab (10 μg) followed by four escalating dosages of postoperative intraperitoneal catumaxomab. Treatment related adverse events (CTC-grade ≥ 3) were frequent (79 versus 37%). This study has thus far only been presented as an abstract and long-term results have not yet been published. The therapeutic value of catumaxomab in the treatment of peritoneal carcinomatosis of gastric cancer is as yet undetermined.

**Discussion**

The ideal drug for intraperitoneal administration should preferably have the following characteristics: first and foremost, the selected drug(s) should have proven activity, both in vitro and in vivo in the treatment of the specific malignancy under study. The drug should have a favorable biodistribution and pharmacokinetic profile and an adequate tissue penetration. Furthermore, drugs for intraperitoneal usage should have a concentration and exposure related cytotoxicity, otherwise intravenous administration may be as effective as intraperitoneal administration. As the rationale for intraperitoneal chemotherapy is based on the peritoneal plasma barrier, the ideal drug should maintain in the peritoneal cavity, for instance by a large molecular weight, preventing diffusion across the peritoneal barrier, allowing high local concentrations of the agent in the peritoneal cavity, without a concomitant increase in the plasma concentration, thus limiting systemic toxicity.

The pharmacokinetic effect of the peritoneal barrier is best expressed by the ratio of the drug’s intraperitoneal area under the concentration–time curve (AUC) to the drug’s plasma AUC. A high intraperitoneal AUC reflects high local exposure and potential efficacy of the drug, while a low plasma AUC indicates low systemic exposure and less systemic toxicity. However, a very high intraperitoneal AUC ratio may reflect inadequate uptake of the drug into cells resulting in insufficient tissue penetration. Adequate tissue penetration can be regarded as the Achilles’ heel of intraperitoneal chemotherapy treatment. The determination of tissue penetration is challenging, but it is generally accepted that the penetration is at best limited to a few millimeters or even a few cell layers. Counter intuitively, the extent of cytoreductive surgery and peritonectomy hardly influences the uptake of intraperitoneal chemotherapy into the systemic circulation. Only large visceral organ resections (e.g., total colectomy and
gastrectomy) lead to a small decrease of systemic uptake of intraperitoneal drugs.\textsuperscript{10} Local and systemic toxicity of the drugs used in HIPEC is inevitable, but should be within acceptable limits. Systemic toxicity frequently consists of bone marrow suppression, and is often dose limiting. Local toxicity can consist of peritoneal sclerosis, increased postoperative bleeding, anastomotic dehiscence, or other tissue healing issues. In reporting local toxicity, it remains difficult whether complications are attributable to the chemotherapeutic agents, or are primarily related to the surgical procedure.

The drug’s mechanism of action as well as its metabolism are of importance. The chemotherapeutic agent should have a direct mechanism of action. For example, a drug that is highly dependent on a specific phase of the cell cycle is undesirable. Likewise, a pro-drug requiring biotransformation before gaining cytotoxicity is unattractive. The metabolism of the drug also influences its pharmacokinetics. Inactivation of a drug after it has left the peritoneal cavity, but before it reaches the systemic circulation, increases the AUC ratio. For example, drugs with extensive first-pass hepatic inactivation have a higher AUC ratio after intraperitoneal perfusion compared to drugs with little inactivation by the liver.\textsuperscript{120}

The characteristics of the carrier solution is a factor to be taken into account in the selection of the agent to be used, as they may influence the pharmacokinetics of the chemotherapy. For instance, isotonic low-molecular weight solutions are rapidly absorbed from the peritoneal cavity, resulting in a decrease of the intraperitoneal volume during intraperitoneal perfusion.\textsuperscript{121} Isotonic saline and dextrose-based dialysis fluids are the most frequently used in HIPEC. The carrier solution should not increase, or may even decrease, the rate of adverse events.

Heat augmentation is a welcome characteristic of a chemotherapeutic drug used for HIPEC. It may be beneficial to its pharmacokinetics, or it may increase cytotoxicity. Hyperthermia is usually added resulting from the increased in vitro cytotoxicity of many chemotherapeutic drugs. Additionally, hyperthermia is believed to have a direct cytotoxic effect. However, the evidence of the clinical benefit of hyperthermia is weak. In one randomized controlled trial, hyperthermic intraperitoneal chemotherapy was superior compared to normothermic intraperitoneal chemotherapy as a prophylactic therapy in advanced gastric cancer patients.\textsuperscript{122} In an animal model with PC from gastric cancer, the combined treatment of hyperthermia and intraperitoneal chemotherapy with mitomycin and cisplatin significantly reduced the extent of peritoneal nodules and increased the mean survival time compared to chemotherapy or hyperthermia alone.\textsuperscript{123}
The drug, or combination of drugs, has to be safely applicable during the operation. A highly volatile drug, or combination of drugs, is unwanted since it may form a health risk to the surgical personnel. Resulting from systemic results in various malignancies, including gastric cancer, a combination of drugs will probably result in a higher efficacy compared to monotherapy. Additionally, in colorectal cancer a combination of drugs in HIPEC has been shown to have a superior effect compared to single-agent therapy. When a combination of drugs is used, there needs to be at least an additive, but preferably a synergistic, effect based on different mechanisms of action of the applied chemotherapy.

Studies to date

Most studies on intraperitoneal chemotherapy in gastric cancer have been performed in Asia, where the incidence of gastric cancer far exceeds that in Western countries. The tumor biology of gastric cancer significantly differs between Asia and Western countries which makes the comparison of treatment results difficult. Previous studies have shown a favorable effect of HIPEC in gastric cancer patients both in the prophylactic and therapeutic setting, but comparison between studies is hampered by the wide range of HIPEC techniques, chemotherapeutic agents, doses, temperatures, and duration of perfusion used in these studies. The longest survival, as in other peritoneal surface malignancies treated with HIPEC, is shown in patients after complete cytoreduction.

The largest Western patient series has been a retrospective cohort of 159 patients with peritoneal carcinomatosis (PC) from gastric cancer treated with HIPEC using various chemotherapeutic drugs, with open (coliseum) and closed techniques, intraoperative or early postoperative intraperitoneal chemotherapy over a period of 18 years, and thus recommendations for daily clinical practice could not be made. In a recent meta-analysis of prophylactic HIPEC, all studies originated from China and Japan. In various concentrations mitomycin, cisplatin, and 5-FU, or combinations of these, were administered for 50–120 min with temperatures varying between 41 °C and 50 °C. An overall survival improvement was established in the HIPEC group (relative risk (RR): 0.73, 95% confidence interval (CI) 0.64–0.83, P < 0.00001).

In patients with manifest peritoneal carcinomatosis one randomized controlled trial has been published, Yang et al. randomized 68 patients with gastric cancer either to CRS or to CRS + HIPEC. The perfusion time was 60–90 min using cisplatin 120 mg and mitomycin 30 mg each in 6 L of normal saline at 43 ± 0.5 °C. A significant median survival benefit
was shown in the CRS + HIPEC group compared to CRS alone (11.0 versus 6.5 months, P = 0.046). A meta-analysis of the studies on HIPEC in established PC showed a median survival varying between 6.1 months and 11.5 months after HIPEC, with a median survival of up to 43.4 months in patients with complete cytoreduction.\textsuperscript{128} Again, a wide range of HIPEC techniques, perfusion times, and temperatures was used with mitomycin C, cisplatin, paclitaxel, etoposide, oxaliplatin, irinotecan, fluorouracil, or a combination of these. Table 1 gives an overview of studies of intraoperative intraperitoneal hyperthermic chemotherapy for gastric cancer, which included at least ten patients.\textsuperscript{8,13,101-105,122,127,129-146}

**Ongoing studies**
Currently, several studies are investigating the role of HIPEC in gastric cancer patients using several chemotherapeutic regimes. The GASTRICHIP study (NCT01882933) is a multicenter randomized phase III trial comparing curative gastrectomy with or without HIPEC with oxaliplatin in patients with advanced gastric adenocarcinoma (T3, T4 and/or N+ and/or with positive peritoneal cytology). Another study initiated in China investigates the survival and toxicity of HIPEC with oxaliplatin and paclitaxel in patients with synchronous peritoneal metastases (NCT01471132). In Germany, a randomized controlled trial was initiated in August 2012, (NCT01683864) investigating the effect of prophylactic HIPEC with mitomycin and cisplatin in patients with gastric carcinoma (T2–T4, N– or N+, or positive cytology) without proven metastases.

**Future directions**
Presently, systemic treatment, whether (neo)adjuvant in the curative setting or palliative, mostly contains a combination of drugs, which has been shown to have an increased efficacy compared to monotherapy. When considering HIPEC in patients with gastric cancer, it nowadays seems only rational to combine intraperitoneal chemotherapy with systemic treatment. Given the efficacy of present regimens, it appears logical to employ an identical combination of chemotherapy for both intraperitoneal perfusion, and systemic treatment.

Before the onset of randomized trials with HIPEC in gastric cancer phase I-II studies are warranted to establish toxicity profiles and optimal dosing schedules for combinations of chemotherapy. These studies, are presently lacking, and current treatment regimens are mainly based on experimental or empirical data. A regimen consisting of a platinum-based agent and a taxane appears the most promising combination of drugs, as it
has a good systemic effect and the known pharmacokinetic data of intraperitoneal administration are favorable.

Hyperthermic intraperitoneal chemotherapy is a promising treatment option in gastric cancer patients, as many patients develop locoregional and/or peritoneal tumor recurrence. Which chemotherapeutic regime is best has not yet been determined. Ideally, different chemotherapeutic regimes should be compared in a randomized study. However, patient inclusion will be challenging in such trials. The variety in study parameters, including selection of chemotherapeutic agents, dosage, patient characteristics, temperature, duration of perfusion, carrier solution, intraperitoneal pressure, open or closed technique, warrants more experimental and clinical studies to determine the influence of each individual variable on toxicity profile and treatment outcome.
References

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