HIPEC
for ovarian cancer

and the Australian/ New Zealand perspective

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Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC)
Hyperthermia Synergizes with Chemotherapy by Inhibiting PARP1-Dependent DNA Replication Arrest

Lea Schaaf¹, Matthias Schwab¹,², Christoph Ulmer³, Simon Heine¹, Thomas E. Mürdter¹, Jens O. Schmid¹, Georg Sauer⁴, Walter E. Aulitzky⁵, and Heiko van der Kuip¹

Abstract

Although hyperthermia offers clinical appeal to sensitize cells to chemotherapy, this approach has been limited in terms of long-term outcome as well as economic and technical burden. Thus, a more detailed knowledge about how hyperthermia exerts its effects on chemotherapy may illuminate ways to improve the approach. Here, we asked whether hyperthermia alters the response to chemotherapy-induced DNA damage and whether this mechanism is involved in its sensitizing effect in BRCA-competent models of ovarian and colon cancer. Notably, we found that hyperthermia delayed the repair of DNA damage caused by cisplatin or doxorubicin, acting upstream of different repair pathways to block histone polyADP-ribosylation (PARylation), a known effect of chemotherapy. Furthermore, hyperthermia blocked this histone modification as efficiently as pharmacologic inhibitors of PARP (PARPi), producing comparable delay in DNA repair, induction of double-strand breaks (DSB), and cell cytotoxicity after chemotherapy. Mechanistic investigations indicated that inhibiting PARylation by either hyperthermia or PARPi induced lethal DSB upon chemotherapy treatment not only by reducing DNA repair but also by preventing replication fork slowing. Overall, our work reveals how PARP blockade, either by hyperthermia or small-molecule inhibition, can increase chemotherapy-induced damage in BRCA-competent cells.

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The Role of Heated Intraperitoneal Chemotherapy (HIPEC) in Ovarian Cancer: Hope or Hoax?

Thomas J. Herzog, MD, FACS

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1st Evidence-based Italian consensus conference on cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinosis from ovarian cancer

Davide Cavaliere, Roberto Cirocchi, Federico Coccolini, Anna Fagotti, Massimiliano Fambrini, Orietta Federici, Domenica Lorusso, Marco Vaia, Marco Ceresoli, Paolo Delrio, Alfredo Garofalo, Sandro Pignata, Paolo Scollo, Vito Trojano, Andrea Amadori, Luca Ansaloni, Giuseppe Cariti, Franco De Cian, Pierandrea De Iaco, Michele De Simone, Marcello Deraco, Annibale Donini, Giammaria Fiorentini, Luigi Frigerio, Stefano Greggi, Antonio Macri, Enrico Maria Pasqual, Franco Rovilino, Paolo Sammartino, Cinzia Sassaroli, Giovanni Scambia, Carlo Staudacher, Patrizia Vici, Enrico Vizza, Mario Valle; On behalf of the Italian Society of Surgical Oncology (SICO), the Italian Society of Obstetrics and Gynaecology (SIGO), the Italian Association of Hospital Obstetricians and Gynaecologists (AOGOI), and the Italian Association of Medical Oncology (AIOM)
HIPEC for advanced epithelial ovarian cancer: What gynaecological oncologists really think
Farrell R ANZJOG 2019

Table 4: Reasons why a gynaecological oncologist would not refer a patient with advanced epithelial ovarian cancer for heated intraperitoneal chemotherapy (HIPEC) (n=46)

<table>
<thead>
<tr>
<th>Reason(s)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is not enough evidence to support HIPEC</td>
<td>33(72)</td>
</tr>
<tr>
<td>You are concerned about potential morbidity and mortality</td>
<td>23(50)</td>
</tr>
<tr>
<td>You are concerned about negative effect on quality of life</td>
<td>16(35)</td>
</tr>
<tr>
<td>You do not think it is superior to (normothermic post-operative) Intraperitoneal chemotherapy</td>
<td>12(26)</td>
</tr>
<tr>
<td>You do not think it is superior to intravenous chemotherapy</td>
<td>12(26)</td>
</tr>
<tr>
<td>There is no HIPEC service in your hospital/city</td>
<td>4(9)</td>
</tr>
</tbody>
</table>
Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer

Willemien J. van Driel, M.D., Ph.D., Simone N. Koole, M.D., Karolina Sikorska, Ph.D., Jules H. Schagen van Leeuwen, M.D., Ph.D., Henk W.R. Schreuder, M.D., Ph.D., Ralph H.M. Hermans, M.D., Ph.D., Ignace H.J.T. de Hingh, M.D., Ph.D., Jacobus van der Velden, M.D., Ph.D., Henriëtte J. Arts, M.D., Ph.D., Leon F.A.G. Massuger, M.D., Ph.D., Arend G.J. Aalbers, M.D., Victor J. Verwaal, M.D., Ph.D., Jacobien M. Kieffer, Ph.D., Koen K. Van de Vijver, M.D., Ph.D., Harm van Tinteren, Ph.D., Neil K. Aaronson, Ph.D., and Gabe S. Sonke, M.D., Ph.D. et al.

January 18, 2018
Effects of CytoReductive surgery plus hyperthermic IntraPEritoneal chemotherapy (HIPEC) *versus* CytoReductive surgery for ovarian cancer patients: A systematic review and meta-analysis

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Figure 1. Number of studies published “hyperthermic” and “peritoneal” and “chemotherapy” on PubMed. Pie chart showing the distribution of each cancer origin of all included papers in this review.
HIPEC studies ongoing in 2018

Ovarian Cancer 2019 update: 21 active studies