mutations) confer a generic sensitivity to DNA-damaging chemotherapy in the neoadjuvant setting and a specific sensitivity to platinum-based chemotherapy in the metastatic setting. It also appears that there are some patients with apparently sporadic TNBC who derive benefit from platinum therapy, both in the neoadjuvant setting as suggested by the GeparSixto study and in the metastatic setting as suggested by the parent study of Zhang et al. The so-called 'genomic scar' assays had utility in predicting response to platinum-based neoadjuvant therapy in at least one study [11], although one such assay did not predict outcome in the TNT study. Recently, interest has grown in defining mutational signatures of HRD through extended genomic sequencing [12, 13], although these are not yet available for routine clinical use. Regretfully, in TNBC, the search continues for an accessible biomarker other than germline *BRCA* mutations to reliably predict platinum response.

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## Funding

None to declare.

## Disclosure

The author has declared no conflicts of interest.

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doi:10.1093/annonc/mdy231
Published online 4 July 2018

## HIPEC: HOPE or HYPE in the fight against advanced ovarian cancer?

Undergoing an era of revolutionary new knowledge and advances in the systemic and surgical treatment of peritoneally disseminated epithelial ovarian cancer (EOC), we never before have been confronted with such a plethora of novel targeted agents, genetically based treatment strategies and cutting edge surgical techniques that enrich our armamentarium in the fight against this deadly disease [1–3]. Still, our art as clinicians is to put all this new body of knowledge into the right context so that we can help our patients without compromising their care through an enthusiastic effort of implementing new therapeutic approaches that are not yet sufficiently validated or confirmed.

A characteristic example of such an enthusiastic endeavor is the incorporation of hyperthermic-intraperitoneal-chemotherapy (HIPEC) in the multimodal treatment concept of advanced EOC. It has already been implemented since years without any acceptable level of evidence from a controlled randomized trial. Has this gap now been closed and is HIPEC ready for prime time?

HIPEC has been developed in an effort to combine the advantages of loco-regional delivery of chemotherapy with surgical radicality [4, 5]. Its application was first described in humans in 1979 in a 35-year-old man with pseudomyxoma peritonei [5]. The presumed benefit is that extensive peritonectomy allows macroscopic cytoreduction of peritoneal implants which, when combined with heated intraperitoneal chemotherapy, provides 'an avenue for further microscopic cytoreduction' as described by Sugarbaker three decades ago [4]. Up to now we did not have any high-quality evidence that HIPEC would positively affect survival in advanced EOC compared with surgery alone. The only prospective randomized trial in the recurrent setting has been widely criticized [6–9], while a large meta-analysis failed to identify any survival benefit [10]. For that reason, HIPEC data were not accepted within the scientific gynecologic oncology community [11]. At the fifth Ovarian Cancer Consensus Conference held

in Tokyo, in November 2015, the recommendation of key opinion leaders was to conduct well-designed clinical trials on important topics in an attempt to establish—or not—any clinical rationale [12].

van Driel and her team published in January 2018 a multicenter, open-label, phase III randomized trial, in which 245 patients with initially presumed inoperable EOC were randomly assigned to undergo or not undergo HIPEC at their interval debulking surgery (IDS), if not having progressed after three cycles of neoadjuvant chemotherapy (NAC) [13]. The study reported a statistically significant progression-free survival (PFS) and overall survival (OS) benefit of HIPEC + IDS without significant increase of surgical morbidity and mortality. Even though these results appear very encouraging and would potentially prompt clinicians and patients to strive a combined maximal surgical effort with HIPEC in all settings of the disease, we agree with the authors of the editorial accompanying the original article [14], that we need to exercise a high degree of caution not to extrapolate to all EOC patients positive data from a study that applies to only a rather small sub-cohort of EOC patients that has significant pitfalls. HIPEC is spreading currently in European and worldwide clinical practice in ovarian cancer without any robust evidence, possibly being harmful for a range of patients, so we need as body of experts to give an evaluation of its presumed merits.

The following shortcomings must be considered:

(1) *Design of the study and end points.* For this type of trial, the primary—or at least co-primary end point should have been OS, in which case the trial would have been larger and reliable enough to exclude significant bias. OS was analyzed at the time when the primary end point PFS was reached. At that time, 44% of the patients were still alive, resulting in 'only' 137 deaths (76 in the control arm and 61 in the HIPEC arm), with a clear imbalance in the PFS/OS improvement ratio: the median OS-benefit was 12 months versus only a 3.5-month PFS-benefit in favor of the HIPEC-arm. The investigators failed to report on other interesting outcome measures such as rates of complete and partial response and details of surgical procedures. We wonder whether the open label study has influenced the surgical quality that is hence difficult to be assessed. Inconsistencies in the determination and description of the actual study design shake additionally the credibility of the study's message: the recruitment database is indicated as closed on 31 March 2017 in the main publication, but on 5 April 2017 in the supplement, while the minimum number of events was reached in April 2016. These inconsistencies rely possibly on the fact that in 2016, directly after end of recruitment, the number of planned patients was decreased with no obvious reason from 280 to 242 [15]. In the original sample size planning, the authors assumed a median PFS of 18 versus 27 months in the two arms. Even though at the final analysis HR was close to what the study investigators expected, the observed median PFS values (10.7 versus 14.2 months) were about half of the initially expected values. Interestingly, some randomizations took place before surgery; the large differences in bowel resection and stoma rates between both arms may therefore be due to a bias of the surgeon already knowing the randomization result.

(2) *Study design addressing only a small population of EOC patients.* The mentioned study defined as eligible patients those with newly diagnosed stage III EOC that were referred for NAC + IDS± HIPEC in specialized centers in the Netherlands because 'their abdominal disease was too extensive for primary cytoreductive surgery or because incomplete surgery was carried out with residual disease >1 cm' [13]. There is, however, no definition of the criteria of inoperability and how patients were allocated to NAC. So, looking at the bigger picture of all advanced EOC patients let us estimate how many of advanced EOC patients this study really addresses. The study excluded all stage IV patients, hence excluding at least one-third of all advanced EOC patients [16]. The investigators did not clarify how they determined or even excluded stage IV disease. With preoperative imaging getting more refined, we diagnose today more commonly stage IV lesions than in the past, with the disease often remaining resectable after all, as for example in the case of extra-abdominal lymph nodes and parenchymatous liver- or spleen-metastases [17, 18]. From the two-thirds remaining patients; ∼10% will be fragile with a poor performance status unable to undergo radical surgical cytoreduction, even less with the addition of HIPEC [19]. That leaves us with less than ∼50% of all advanced EOC patients. From those, the majority can be cytoreduced to ≤10 mm residual disease in an upfront setting in appropriately trained and specialized cancer centers [19–21], leaving us with <10% of all patients with advanced EOC that would theoretically fulfill the eligibility criteria of the van Driel study. The 'super-selection' of patients in this trial is reflected in the fact that even though mainly large volume and highly specialized cancer centers participated in this study, only an average of 3.5 patients per year per center were recruited [13]. How justified would it be to extrapolate data that theoretically affect a minority of the entire patients' population to all EOC patients and generically claim that HIPEC has now an established value and survival benefit in the multimodal management of this challenging disease?

(3) *Heterogeneity of the results between the various study centers.* A 43% of the patients were recruited by one center alone, namely the Netherlands Cancer Institute with the recruitment numbers of the remaining centers being comparatively small (see Figure 1). The study did not account for such small recruitment numbers and given the overall limited patients number, a spread within many small centers led to imbalances despite randomization. The fact that the study did not stratify for important prognosticators such as BRCA-status or histologic subtype further aggravate this. A forest plot for OS showed a favor of HIPEC in non-HGSOC with an HR of 0.31 as opposed to an HR of 0.76 in the HGSOC patients, which is of significant relevance since there is an imbalance of HGSOC and non-HGSOC in the two arms despite randomization.

A further discrepancy we see are the outcomes per individual center reflecting the degree of expertise in a treatment modality not commonly familiar to gynecologic oncologists: the impact of HIPEC was lowest in the most actively recruiting center [13]. In the small recruitment centers—where HR for survival seems more relevant, they did on average only one to two HIPEC cases per year within the study. It is unknown whether the same team would operate in both arms or whether 'HIPEC surgeons' had to step in after randomization to HIPEC.

(4) *Bias of evolving treatment strategies through slow recruitment.* The study seemed to have large difficulties in recruiting since the team needed 9 years to recruit only 245 patients; as opposed to other recent surgical studies in EOC that successfully recruited considerable higher number of patients in shorter

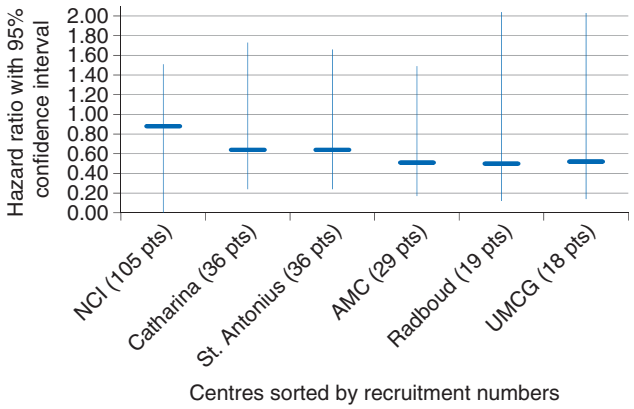


**Figure 1.** Hazard ratios (HR) and recruitment numbers per center of note; two further centers recruiting only one patient each (Antwerp and CMSE) not included.

time periods; e.g. the AGO-DESKTOP-study (ENGOT-ov20; NCT01166737) recruited 408 patients within 4.5 years and the LION-study (AGO-OVAR OP3/ENGOT-ov31) 650 patients in only 3 years [22, 23]. This large discrepancy in recruitment and completion of the trial may be interpreted as surrogate marker for the quality of the study and the presence of strong selection bias. Most importantly, treatment modalities and surgical techniques change and evolve over the time period of a decade.

(5) *Underreported toxicity*. Surprisingly, the authors report equivalent toxicity in both arms, even though the HIPEC patients received one additional course of cisplatin chemotherapy. Furthermore, the operation time was almost doubled in the HIPEC arm, with longer hospital stays and higher costs. A 4% of the patients in the HIPEC-arm underwent a gastrostomy; a very rare and morbid event in primary EOC-surgery. We wonder why no established surgical morbidity classification score (e.g. Clavien–Dindo) was used to report on these specific adverse events. Among patients who underwent a bowel resection, a stoma formation was carried out in 72% in the HIPEC-group as opposed to 43% in the surgery only group [13]. The formation of a stoma is one of the main factors potentially affecting postoperative QoL. Furthermore, with stoma formation being associated with longer term complications such as herniation, fistulation, stenosis etc. [24] there is the risk of precluding those patients from receiving adjuvant treatment with antiangiogenetic targeted agents such as bevacizumab, which have been proved to significantly influence disease control in patients with high tumor load and residual disease [25]. Even though QoL-measurements did not seem to be overall negatively affected by the addition of HIPEC, we question why QoL and a surgical complication classification were not reported in detail in the van Driel study.

The initially presumed survival benefit of intraperitoneal chemotherapy in EOC seem to have been over-ranked by newly emerging targeted therapies that are given systemically in a maintenance regimen. A good example is the GOG 252 study, where intraperitoneally applied cytotoxic chemotherapy failed to achieve any survival benefit in a multimodal treatment concept with systemic maintenance bevacizumab [26].

The results of the van Driel study are in contradiction with the recent results from the multicenter prospective randomized HIPEC-study by Lim and Bristow, which was also presented at ASCO 2017 and which was negative for both PFS and OS [27]. The difference between the two studies was that the Lim study had broader inclusion criteria allowing also upfront cytoreduction (only 39% received NAC), as long as postoperative residual disease was <1 cm. But even when evaluating the NAC patients separately, the median PFS for HIPEC- and control-group were 20 and 18 months ($P = 0.137$) with a median OS of 54 and 51 months ($P = 0.407$), respectively, and hence also not significantly different. The Lim study addressed a much larger patients' population than the van Driel one and was therefore much closer to the reality of the everyday treated EOC patients.

Nevertheless, the colleagues who ran the Dutch HIPEC-trial in EOC deserve recognition for having conducted the first phase III randomized HIPEC-trial in a challenging patients' collective with initially inoperable stage III disease. We just need to be careful not to extrapolate these results to all advanced EOC patients. We must question ourselves as gynecologic oncology society whether the personal, financial and infrastructural resources that we are called to invest in an effort to maximize surgical benefit, is worth investing in broadly implementing HIPEC facilities or rather in training and implementing centralized centers and teams qualified to perform maximal effort cytoreductive surgery in and outside the peritoneal cavity in combination with novel systemic and maintenance regimens [28]. This is an answer that we might obtain when the TRUST-trial (AGO-OVAR-OP.7, NCT02828618) will be reported [29]. In the meantime, we cannot and should not as body of experts recommend implementation of HIPEC in the surgical treatment of all advanced EOC patients.

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## Funding

None declared.

## Disclosure

The authors have declared no conflicts of interest.

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doi:10.1093/annonc/mdy198
Published online 4 June 2018

## PARPi related toxicities: do we need more appropriate instruments to evaluate it?

The development of poly(ADP-ribose) polymerase inhibitors (PARPi) for therapy is a successful application of bench-to-bedside medicine and at present represents a major breakthrough in ovarian cancer care.

Almost half of all ovarian cancers present deficiencies in the homologous recombination (HR) DNA repair pathway and PARP inhibitors are being utilized in the clinic to manage recurrent ovarian cancers that display defects in the HR repair pathway. However, PARP inhibitors have also shown significant clinical benefit in patients without HR deficiencies [1].

Between December 2014 and July 2017, three PARPi (olaparib, rucaparib, and niraparib) were licensed for the treatment of recurrent ovarian cancer and approvals for additional disease indications are anticipated. Olaparib received FDA approval as monotherapy in *BRCA* mutated ovarian cancer who had received at least three previous chemotherapy lines [2] and as maintenance in platinum sensitive, platinum responsive ovarian cancer patients' regardless *BRCA* mutation [3]. EMA approval of Olaparib is limited to the maintenance treatment of *BRCA* mutated, platinum sensitive, recurrent ovarian cancer patients who had responded to platinum-based chemotherapy. FDA approval of rucaparib as monotherapy in *BRCA* mutated patients who had received at least two previous chemotherapy lines was announced