Critical Reviews in Oncology / Hematology 143 (2019) 14–19

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Hopes and failures in front-line ovarian cancer therapy

Irina Tsibulak, Alain G. Zeimet, Christian Marth*

Department of Obstetrics and Gynecology, Medical University of Innsbruck, Innsbruck, Austria

ARTICLE INFO

Keywords:
Ovarian cancer
Front-line therapy
Overall survival
Systemic therapy
Maintenance

ABSTRACT

Through the last three decades, the combination of paclitaxel and carboplatin remains the standard of care chemotherapy in newly diagnosed epithelial ovarian cancer (EOC). Based on a single trial, first-line maintenance therapy with angiogenesis inhibitor bevacizumab was approved in Europe and widely applied. In 2018, based on a second trial bevacizumab was approved for first-line maintenance in the United States. Despite complete remission upon chemotherapy, the majority of the patients recur. A large number of randomized trials were conducted to explore the optimal front-line therapy regimen, but neither dose-densing, nor adding of a third chemotherapy agent or intraperitoneal administration could improve overall survival (OS). Also implementation of hyperthermic intraperitoneal chemotherapy (HIPEC) or the neoadjuvant approach failed to improve OS.

Recently, maintenance therapy with PARP inhibitors showed encouraging results in patients with BRCA1/2 mutation. Further trials with targeted therapies are ongoing.

Here we review the achievements of front-line therapy in primary advanced EOC through the last three decades and discuss future treatment strategies.

1. Introduction

Epithelial ovarian cancer (EOC) is one of the leading causes of cancer death in women in the western world. It is most likely to be diagnosed at advanced stage, therefore requiring aggressive cytoreductive surgery and systemic adjuvant or neoadjuvant chemotherapy. Even despite complete resection and complete remission upon chemotherapy, the majority of the patients recur. Thus, the concept of the maintenance therapy to prolong the progression-free interval (PFI) as well as overall survival (OS) was introduced and established. A plethora of well-designed randomized trials explored the optimal front-line chemotherapy regimen, the benefit of neoadjuvant systemic therapy as well as the impact of the maintenance therapy in the treatment of advanced EOC. However, despite considerable advances in the prolongation of the time to first progression, overall survival remains poor and EOC patients are still succumbing to this disease.

Here we review the achievements of front-line treatment strategies in primary advanced EOC and their impact on patients' survival through the last three decades (Table 1 and Fig. 1).

2. Early 1990s

2.1. Standard of care first-line chemotherapy

The present standard of care in front-line therapy of EOC is the combination of paclitaxel 175 mg/m^2 and carboplatin area under the curve (AUC) 5 or 6, administered intravenously every 3 weeks (du Bois et al., 2005).

Two large randomized clinical trials demonstrated a better OS for patients with advanced EOC on the paclitaxel-cisplatin regimen than on the at that time standard cyclophosphamide-cisplatin regimen, reporting median OS of 38 versus 24 months in the Gynecologic Oncology Group (GOG) 111 Trial and 35.6 versus 25.8 months in the confirmatory European and Canadian Intergroup Trial (McGuire et al., 1996; Piccart et al., 2000). Two other trials followed, replacing cisplatin by carboplatin and confirming the comparable efficacy (median OS 43.3 vs. 44.1 and 57.4 vs. 48.7 months, respectively) but a better tolerability of carboplatin (du Bois et al., 2003; Ozols et al., 2003). Since the end of the 1990s, several further trials have tried to improve the OS by adding a third drug such as topotecan, epirubicin or gemcitabine to the standard regimen or by substitution of paclitaxel by docetaxel or pegylated liposomal doxorubicin. However, none of them was able to obtain superior results, and revealed a range of 33–61.6 months in the median OS depending on FIGO stage and residual disease after surgery

* Corresponding author at: Department of Obstetrics and Gynecology, Medical University Innsbruck, Anichstrasse 35, A-6020 Innsbruck, Austria.
E-mail addresses: irina.tsibulak@i-med.ac.at (I. Tsibulak), alain.zeimet@i-med.ac.at (A.G. Zeimet), christian.marth@tirol-kliniken.at (C. Marth).

https://doi.org/10.1016/j.critrevonc.2019.08.002
Received 19 March 2019; Received in revised form 7 August 2019; Accepted 9 August 2019

Table 1
Reported Median Overall Survival in Phase III Trials in Advanced Ovarian Cancer.

Study	n	FIGO stage	control arm	study arm	median OS (months)	recruitment start
Front-line chemotherapy in ovarian cancer						
GOG-111 (McGuire et al., 1996)	386	III-IV	Cisplatin/Cyclophosphamid	Cisplatin/Paclitaxel	38.0 vs. 24.0	1990
OV10/European-Canadian Intergroup Trial (Piccart et al., 2000)	680	IIb-IV	Cisplatin/Cyclophosphamid	Cisplatin/Paclitaxel	25.8 vs. 35.6	1994
AGO-OVAR3 (du Bois et al., 2003)	798	IIb-IV	Cisplatin/Paclitaxel	Carboplatin/Paclitaxel	44.1 vs. 43.3	1995
GOG-158 (Ozols et al., 2003)	792	III	Cisplatin/Paclitaxel	Carboplatin/Paclitaxel	48.7 vs. 57.4	1995
AGO-OVAR5 (du Bois et al., 2006)	1253	IIb-IV	Carboplatin/Paclitaxel	Carboplatin/Paclitaxel/Epirubicin	45.8 vs. 41.0	1997
SCOTROC (Vasey et al., 2004)	1077	Ic-IV	Carboplatin/Paclitaxel	Carboplatin/Docetaxel	34.5 vs. 33	1998
NSGO-EORTC GCG-NCIC CTG-GEICO (Lindemann et al., 2012)	887	IIb-IV	Carboplatin/Paclitaxel	Carboplatin/Paclitaxel/Epirubicin	40.2 vs. 42.4	1999
AGO-OVAR7 (Pfisterer et al., 2006)	1289	IIb-IV	Carboplatin/Paclitaxel	Carboplatin/Paclitaxel/Topotecan	43.1 vs. 44.5	1999
GOG-182-ICON5 (Bookman et al., 2009)	4312	III-IV	Carboplatin/Paclitaxel	CPG; CPD; CT-CP; CG-CP[a]	40.7 vs. 42 vs. 44.2 vs. 40 vs. 39.6	2001
NCIC-EORTC-GEICO OV16 (Cervantes-Ruiperez et al., 2013)	819	IIb-IV	Carboplatin/Paclitaxel	Cisplatin/Topotecan + Carboplatin/Paclitaxel	44.8 vs. 44.2	2001
AGO-OVAR9 (du Bois et al. 2010)	1585	Ic-IV	Carboplatin/Paclitaxel	Carboplatin/Paclitaxel/Gemcitabine	51.5 vs. 49.5	2002
MITO-2 (Pignata et al., 2011)	801	Ic-IV	Carboplatin/Paclitaxel	Carboplatin/Pegylated liposomal doxorubicin (PLD)	53.2 vs. 61.6	2003
NOVEL/JGOG-3016 (Katsumata et al., 2013)	631	II-IV	Carboplatin/Paclitaxel	Carboplatin/dose-dense weekly Paclitaxel	62.2 vs. 100.5	2003
MITO-7 (Pignata et al., 2014)	810	Ic-IV	Carboplatin/Paclitaxel	Carboplatin/dose-dense weekly Paclitaxel	no data vs. 48.0	2008
GOG-262 (Chan et al., 2016)	692	II-IV	Carboplatin/Paclitaxel ± Bevacizumab	Carboplatin/dose-dense weekly Paclitaxel ± Bevacizumab	39.0 vs. 40.2	2010
Secondary cytoreductive surgery						
EORTC-55865 (van der Burg et al., 1995)	319	IIb-IV	PDS + chemotherapy only	secondary cytoreductive surgery	20.0 vs. 26.0	1987
GOG-152 (Rose et al., 2004)	448	III-IV	PDS + chemotherapy only	secondary cytoreductive surgery	33.7 vs. 33.9	1994
Inhibition of angiogenesis & maintanance therapy						
GOG-218 (Burger et al., 2018)	1873	III-IV	Placebo	5xBevacizumab vs. 21xBevacizumab	40.6 vs. 38.7 vs. 43,8	2005
ICON-7 (Perren et al., 2011)	1528	III-IV	Placebo	Bevacizumab	28.8 vs. 36.6	2006
AGO-OVAR16 (Vergote et al., 2018)	940	II-IV	Placebo	Pazopanib	64.0 vs. 59.1	2007
AGO-OVAR12 (du Bois et al. 2016)	1366	IIb-IV	Placebo	Nintenanib	62.8 vs. 62.0	2009
TRINOVA-3 (Vergote et al., 2016)	1015	III-IV	Placebo	Trebananib	43.6 vs. 46.6	2012
Primary debulking surgery (PDS) vs.neoadjuvant chemotherapy (NACT) + interval debulking surgery (IDS)						
EORTC (Vergote et al., 2010)	632	IIIc-IV	PDS	NACT + IDS	29.0 vs. 30.0	1998
CHORUS (Kehoe et al., 2015)	550	III-IV	PDS	NACT + IDS	22.6 vs. 24.1	2003
JCOG-602 (Onda et al., 2018)	301	III-IV	PDS	NACT + IDS	49.0 vs. 44.3	2006
SCORPION (Fagotti et al., 2018)	171	IIIc-IV	PDS	NACT + IDS	41.0 vs. not reached	2011
Intraperitoneal (i.p.) chemotherapy						
SWOG-8501/GOG-104 (Alberts et al., 1996)	546	III	i.v. Cisplatin/i.v. Cyclophosphamide	i.p. Cisplatin/i.v. Cyclophosphamide	41.0 vs. 49.0	1986
SWOG-9227/GOG-114 (Markman et al., 2001)	462	III	i.v. Cisplatin/i.v. Paclitaxel	i.v. Carboplatin/i.p. Cisplatin/i.v. Paclitaxel	63.0 vs. 52.0	1992
GOG-172 (Armstrong et al., 2006)	415	III	i.v. Cisplatin/i.v. Paclitaxel	i.p. Cisplatin/i.p. Paclitaxel/i.v. Paclitaxel	49.5 vs. 66.9	1998
GOG-252 (Walker et al., 2016)	1560	II-III	i.v. Paclitaxel/i.v. Carboplatin/i.v. Bevacizumab	i.v. Paclitaxel/i.p. Carboplatin/i.v. Bevacizumab or i.v. Paclitaxel/i.p. Cisplatin/ i.p. Paclitaxel/i.v. Bevacizumab	no data	2009
Hyperthermic intraperitoneal chemotherapy (HIPEC)						
OVHIPEC (van Driel et al., 2018)	245	III	NACT + IDS + no HIPEC	NACT + IDS + HIPEC	33.9 vs. 45.7	2007
Korean HIPEC study (Lim et al., 2017)	184	III-IV	PDS + no HIPEC + adjuvant chemotherapy	PDS + HIPEC + adjuvant chemotherapy	51 vs. 54	2010

[a]CPG = Carboplatin/Paclitaxel/Gemcitabine; CPD = Carboplatin/Paclitaxel/PEG-Doxorubicin; CT-CP = Carboplatin/Topotecan, then Carboplatin/Paclitaxel; CG-CP = Carboplatin/Gemcitabine, then Carboplatin/Paclitaxel.

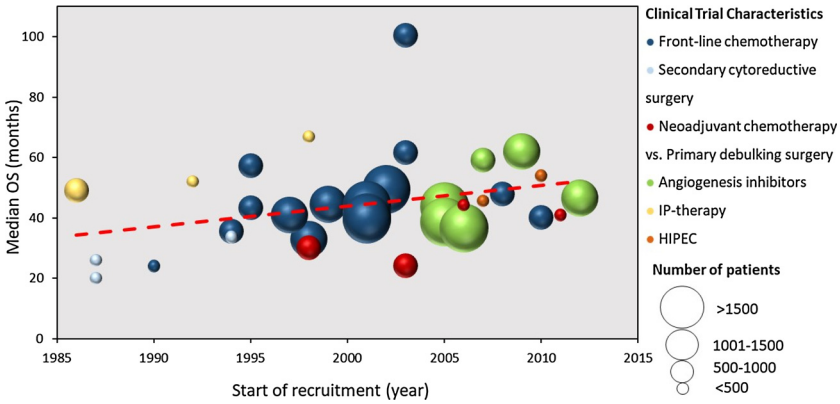

Fig. 1. Reported Median Overall Survival in Experimental Arms of Phase III Trials in Advanced Ovarian Cancer.
Each circle represents a phase III clinical trial on newly diagnosed advanced ovarian cancer and its size represents number of enrolled patients. The Y axis shows median overall survival in months, the X axis shows year of trials' start of randomization.

(Vasey et al., 2004; du Bois et al., 2006; Pfisterer et al., 2006; Bookman et al., 2009; du Bois et al., 2010; Pignata et al., 2011; Lindemann et al., 2012; Cervantes-Ruiperez et al., 2013).

2.2. Secondary cytoreductive surgery as part of front-line therapy

In early 1990s two randomized phase III trials investigated the benefit of secondary cytoreducitve surgery as part of first line therapy in advanced EOC. In the EORTC-55865 trial patients, who had more than 1 cm residual lesions after primary surgery were included. After three cycles of cyclophosphamide and cisplatin they were randomized to undergo either secondary cytoreductive surgery or no surgery, followed by further chemotherapy. The reported OS benefit was six months in the secondary debulking surgery group (20 vs. 26 months). This benefit was even more impressive when patients with FIGO stage IV were excluded (van der Burg et al. 1995). However, these results could not been confirmed in the GOG-152 trial. The design of that study was similar to EORTC-55865, the used chemotherapy regimen was the combination of paclitaxel and cisplatin and the reported OS was 10.5 versus 10.7 months. Based on these data, it can be concluded that secondary cytoreductive surgery does not improve survival in patients who underwent a serious effort for optimal primary debulking surgery in specialized gynecologic oncological centers (Rose et al., 2004).

3. Late 1990s: intraperitoneal therapy

The principal site of disease in EOC is the peritoneal cavity. Therefore, regional therapy through intraperitoneal (i.p.) administration has been considered in the late 1990s (Alberts et al., 1996; Markman et al., 2001). GOG-172 was a large-scale phase III trial and reported OS improvement of 15.9 months (65.6 months vs. 49.7 months) in the i.p. arm (135 mg of intravenous (i.v.) paclitaxel per square meter of body-surface area over a 24 -h period followed by 100 mg of i.p. cisplatin per square meter on day 2 and 60 mg of i.p. paclitaxel per square meter on day 8) in comparison to i.v. (135 mg of i.v. paclitaxel per square meter of body-surface area over a 24 -h period followed by 75 mg of i.v. cisplatin per square meter on day 2) arm. However, only 42 percent of the patients in the i.p.-therapy arm completed six cycles of the assigned therapy due to increased toxicity and catheter-related complications. Therefore, the use of i.p. chemotherapy has not been universally accepted (Armstrong et al., 2006).

More recently, GOG-252 trial failed to show a survival benefit in i.p. cisplatin and i.p. carboplatin group over dose-dense intravenous paclitaxel and carboplatin (no OS analysis provided). However, it is important to notice, that in this trial bevacizumab was incorporated in all arms of the study (Walker et al., 2016). Therefore, this antiangiogenic agent may have neutralized the clinical advantage of i.p. chemotherapy.

4. Early 2000s: dose-dense and neoadjuvant chemotherapy

Concepts to optimize chemotherapy have also included dose-dense weekly scheduling of paclitaxel. The strategy of dose dense chemotherapy showed a longer PFI (28.1 vs. 17.5 months) as well as better median OS (100.5 vs. 62.2 months) in the NOVEL trial by Japanese Gynecologic Oncology Group (Katsumata et al., 2013). Nonetheless, these results could not be confirmed for the Western population in the GOG-262 Trial (median 40.2 vs. 39.0 months) (Chan et al., 2016). Notably, 84% of patients in GOG-262 received bevacizumab. Interestingly, in a subgroup analysis in patients who did not receive bevacizumab, weekly paclitaxel was associated with better PFS than paclitaxel administered every 3 weeks (14.2 vs. 10.3 months). In contrast, among patients who received bevacizumab, weekly paclitaxel did not significantly prolong PFS, as compared with paclitaxel administered every 3 weeks (14.9 months vs. 14.7 months).

The ICON-8 results were presented on ESMO 2017 Congress in Madrid and demonstrated that weekly paclitaxel as part of the first-line treatment of EOC did not prolong PFS (median PFS 24.4 months with standard dosing vs. 24.9 and 25.3 months in study arms) (Clamp et al., 2017).

Multicenter Italian Trials in Ovarian cancer and gynecologic malignancies (MITO) group evaluated a chemotherapy regimen with weekly carboplatin (AUC 2) plus weekly paclitaxel (60 mg/m^2) for 18 weeks in comparison with carboplatin/paclitaxel every three weeks and reported similar PFS of 18.3 months vs. 17.3 months, respectively (Pignata et al., 2014).

The most important independent prognostic factor for OS is still the achievement of no residual tumor after primary debulking surgery (PDS) (Vergote et al., 2011). However, some patients will still have bulky residual tumor after surgery, even if they have been treated in specialised gynecologic oncology centers. Therefore, an alternative strategy with neoadjuvant chemotherapy (NAC) followed by interval debulking surgery has been taken into consideration in order to achieve higher complete resection rates in patients with extensive stage IIIc and IV EOC. In 2010 the results of the EORTC trial 55971 were published, reporting similar median OS (30 months in the NAC group vs. 29 months in the PDS group) and the median PFS of 12 months in both groups (Vergote et al., 2010). These results were confirmed in the CHORUS trial, published 5 years later (median OS of 24.1 months in NAC group vs. 22.6 months in the PDS group) (Kehoe et al., 2015). In fact, both trials showed that the NAC followed by interval debulking surgery (IDS) was not inferior to PDS followed by chemotherapy in patients with stage III or IV EOC. In addition, less complications and a lower postoperative mortality was reported for NAC group in both studies. Thus, this strategy can be a better alternative treatment in patients with non-resectable disease but does not improve either the PFS or OS. Two further studies on neoadjuvant treatment were presented at ASCO Annual Meeting 2018. JCOG-602 was a non-inferiority trial with patients randomized to PDS arm (PDS followed by 8 cycles of

paclitaxel and carboplatin) and NAC arm (4 cycles of paclitaxel and carboplatin, IDS, 4 cycles of paclitaxel and carboplatin). Median PFS was 15.1 months for PDS arm and 16.4 months for NAC arm, median OS was 49.0 months in PDS arm and 44.3 months in NAC arm, so that the non-inferiority of NAC could not be confirmed in this study (Onda et al., 2018). SCORPION trial was a superiority, randomized phase III trial. No significant difference was seen for PFS; median OS was 41 months in the PDS arm and not reached in the NAC arm (overall median FU was 42 months). In terms of PFS, NAC was not superior to PDS in this trial (Fagotti et al., 2018). However, median duration of surgery as reported in the majority of these trials calls into question the quality of surgical attempts to reach complete tumor resection. Therefore, AGO Germany launched the ongoing TRUST Trial conducted in selected high volume expert centers, aiming to determine the optimal timing of surgery (primary- or interval debulking) within the therapeutic procedures in patients with advanced ovarian cancer who in fact underwent high-end surgical treatment (Mahner et al., 2017).

5. Late 2000s: the era of anti-angiogenic therapy

A necessary step of tumor proliferation and invasion is neoangiogenesis. Vascular endothelial growth factor (VEGF) is the most important proangiogenic factor and an important promoter of progression in EOC (Belotti et al., 2008). The role of bevacizumab in the front-line and maintenance therapy of ovarian cancer was explored in two large prospective randomized trials.

The GOG-218 trial was a double-blind 3-arm clinical trial with PFS as primary endpoint. All patients enrolled in the study (stage III and IV disease with residual macroscopic tumor after debulking surgery) received standard chemotherapy with intravenous paclitaxel and carboplatin administered every 3 weeks for 6 cycles, and were randomized to one of the following 3 arms: the control arm with intravenous placebo in cycles 2 to 22; the bevacizumab-initiation arm with administration of bevacizumab 15 mg/kg every 3 weeks in cycles 2 to 6, followed by placebo from cycles 7 to 22; and the bevacizumab-throughout arm with administration of bevacizumab in cycles 2 to 6 and followed by a maintenance therapy from cycles 7 to 22. The bevacizumab-throughout arm had a significantly longer PFS than the control arm (14.1 vs. 10.3 months). No significant benefit was shown in the bevacizumab-initiation arm compared with the control arm. However, the median OS was similar in all arms: 40.6 vs. 38.7 vs. 43.8 months for the control arm, the bevacizumab-initiation arm and the bevacizumab-throughout arm, respectively (Burger et al., 2011, 2018).

The ICON-7 trial was a 2-arm trial and included patients with high risk FIGO stage I (defined as grade 3 or clear cell histology) to stage IV EOC. The control group received standard chemotherapy with paclitaxel and carboplatin administered every 3 weeks; and the experimental group received the same chemotherapy regimen with bevacizumab 7.5 mg/kg every 3 weeks added from cycles 1 to 18. The median PFS at 42 months was 22.4 months without bevacizumab versus 24.1 months with bevacizumab and there was no significant difference in OS. However, the benefit was greater in patients at high risk for progression (defined as FIGO stage IV or FIGO stage III and > 1.0 cm of residual tumor after debulking surgery), with median PFS of 14.5 months without bevacizumab versus 18.1 months with bevacizumab. The respective median OS was 28.8 months versus 36.6 months, showing a significant benefit of bevacizumab therapy for patients at high risk of progression (Perren et al., 2011).

Besides bevacizumab, other antiangiogenic agents were investigated in the treatment of EOC. Pazopanib is an oral tyrosine kinase inhibitor of VEGF receptors (VEGFR) -1, -2, and -3, platelet-derived growth factor receptors (PDGFR) -α and -β and c-KIT. Pazopanib was investigated as maintenance therapy in AGO-OVAR-16 trial. This study included patients with FIGO stage II-IV EOC without progression after debulking surgery and first-line platinum-taxane chemotherapy, randomized to placebo or pazopanib arm for up to 24 months. The primary endpoint was the PFS, showing a statistically significant PFS improvement of 5.6 months (17.9 months vs. 12.3 months), but no benefit in OS (59.1 vs. 64 months) (du Bois et al., 2014; Vergote et al., 2018).

Nintedanib is a potent oral inhibitor of the VEGFR-1, -2 and -3, fibroblast growth factor receptors (FGFRs) and PDGFR-α and -β. Nintedanib was investigated in the AGO-OVAR12 phase III trial, which included patients with FIGO stage IIb-IV EOC after primary debulking surgery or only biopsy. Patients were randomized to standard paclitaxel/carboplatin chemotherapy for 6 cycles with nintedanib or placebo on days 2–21 of every cycle for up to 120 weeks. A significantly increased PFS from 16.6. to 17.2 months was reported for nintedanib arm. OS data have not been reported yet (du Bois et al., 2016).

Trebananib is a peptide that blocks binding of angiopoietin-1 and -2 to Tie2. The role of trebananib was explored in three TRINOVA studies. However, in the phase III Trinova-3/ENGOT-ov2 trial trebananib plus standard paclitaxel and carboplatin did not show significant survival benefit. The reported OS was 46.6 in the trebananib group versus 43.7 in the control group (Vergote et al., 2016).

6. 2010s: PARP inhibitors

PARP inhibitors showed impressive survival benefits in recurrent EOC (Mirza et al., 2016). Therefore, the role of PARP inhibitors in the front-line maintenance therapy is highly interesting and has led to development of SOLO-1, PAOLA-1, GOG-3005 and PRIMA trials. The results of the first trial, SOLO-1 were published recently. In this study, patients with newly diagnosed advanced EOC and a *BRCA1/2* mutation who have responded to platinum-based chemotherapy were randomized to receive maintenance therapy with olaparib or placebo for 2 years. A substantial PFS benefit was shown in the olaparib group, with a 70% lower risk of disease progression or death than in placebo group (Moore et al. 2018). However, this study evaluated only patients with *BRCA1/2* mutation, who responded to prior platinum-based therapy. It is interesting, if the excellent activity of PARP inhibitors beyond *BRCA1/2* mutation will be also confirmed in the front-line.

7. The present controversy: HIPEC

Another therapeutical approach to treat advanced ovarian cancer is the addition of hyperthermic intraperitoneal chemotherapy (HIPEC) to cytoreductive surgery. This procedure was developed to combine surgical radicality with local delivery of chemotherapy and was adopted from the general surgeons. The most cited study on HIPEC in EOC was a phase III trial by Spiliotis et al., reporting OS improvement of 13.3 months in patients with recurrent EOC undergoing HIPEC (Spiliotis et al., 2015). However, this trial has a lot of limitations regarding statistical analysis, randomization procedures and validity (Harter et al., 2017).

For primary EOC, there are two phase III trials being reported recently. Van Driel et al. investigated whether the addition of HIPEC to IDS would improve outcomes in stage III EOC patients who were receiving NAC. The median PFS was 10.7 months in the surgery group and 14.2 months in the surgery-plus-HIPEC group, the median overall survival was 33.9 months in the surgery group and 45.7 months in the surgery-plus-HIPEC group. These results show a rather uncommon PFS/OS improvement ratio: 3.5 months PFS-benefit, resulting in 12 months OS-benefit (van Driel et al., 2018). However, this study was addressing only a small population of EOC-patients and is in contradiction with the results from the multicenter randomized HIPEC-study by Lim et al., presented at ASCO Annual Meeting 2017 and which was negative for both PFS and OS (Lim et al., 2017).

8. Hope for the future: immune checkpoint inhibitors

There is no more fast-moving field of clinical cancer research than immunotherapy and especially treatment with immune checkpoint

inhibitors. There are already promising results of anti-PD-1-antibodies nivolumab and avelumab in recurrent EOC (Hamanishi et al., 2015; Disis et al., 2016; Marth et al., 2019). The benefit of checkpoint inhibition in the front-line is currently being explored in IMagyn50 (maintenance with bevacizumab and atezolizumab) trial. However, this approach does not seem to be a promising strategy in primary EOC, since the first phase III trial on checkpoint inhibition in primary EOC, JAVELIN Ovarian 100 (chemotherapy and maintenance with avelumab), was closed prematurely, as data from interim analysis did not support the study's hypothesis. The very low mutational burden in EOC precludes presentation of high levels of neo-antigens on cancer cells and thus EOC has to be considered as an immunologically "cold" tumor, supposing low single-agent activity of checkpoint inhibitors. As PARP inhibitors enhance concentrations of free cytoplasmic DNA in cancer cells which is leading to an immune sensing via STING (stimulator of interferon genes) activation, treatment strategies combining immune checkpoint- with PARP inhibitors suggest a strong synergy. Therefore, trials exploring combinations between these two targeted therapies are currently ahead of starting and may require collaborations between pharmaceutical companies, as already seen in TOPACIO/Keynote-162 trial for recurrent EOC (Konstantinopoulos et al., 2018).

9. Conclusion

The combination of paclitaxel and carboplatin administered every there weeks and combined with bevacizumab in patients at high risk of progression with FIGO stage III or higher remains the standard of care front-line therapy for EOC. However, there is no consensus on the duration of the bevacizumab maintenance therapy.

Neither dose-dense, nor adding of a third chemotherapy agent or i.p. administration could improve survival. Implementation of HIPEC or the NAC approach were not superior to the standard chemotherapy.

In summary, for the last 30 years overall survival of EOC patients remains unsatisfactory and we are still failing to cure this disease. At the present time, initial studies are addressing patients with recurrent disease, but the key aim should be finding better treatment strategies in the front-line in order to increase the rate of cure. Further, we should rethink "one-fits-all" standard in the treatment of EOC and need predictive markers to make personalized and targeted therapies as PARP inhibitors and immune checkpoint inhibitors possible in the front-line.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Irina Tsibulak: Roche (honoraria)

Christian Marth and Alain G. Zeimet: EU, Astra Zeneca, Roche (research funding); Roche, Novartis, Amgen, MSD, Pharmamar, Astra Zeneca, Tesaro (honoraria); Roche, Novartis, Amgen, MSD, Astra Zeneca, Pfizer, Pharmamar, Cerulean, Vertex, Tesaro (consultancies).

Declaration of Competing Interest

Irina Tsibulak: Roche (honoraria)

Christian Marth and Alain G. Zeimet: EU, Astra Zeneca, Roche (research funding); Roche, Novartis, Amgen, MSD, Pharmamar, Astra Zeneca, Tesaro (honoraria); Roche, Novartis, Amgen, MSD, Astra Zeneca, Pfizer, Pharmamar, Cerulean, Vertex, Tesaro (consultancies).

References

Alberts, D.S., Liu, P.Y., Hannigan, E.V., O'Toole, R., Williams, S.D., Young, J.A., et al., 1996. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. N. Engl. J. Med. 335 (26), 1950–1955.

Armstrong, D.K., Bundy, B., Wenzel, L., Huang, H.Q., Baergen, R., Lele, S., et al., 2006. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N. Engl. J. Med. 354 (1), 34–43.

Belotti, D., Calcagno, C., Garofalo, A., Caronia, D., Riccardi, E., Giavazzi, R., Taraboletti, G., 2008. Vascular endothelial growth factor stimulates organ-specific host matrix metalloproteinase-9 expression and ovarian cancer invasion. Mol. Cancer Res. 6 (4), 525–534.

Bookman, M.A., Brady, M.F., McGuire, W.P., Harper, P.G., Alberts, D.S., Friedlander, M., et al., 2009. Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: a phase III trial of the gynecologic cancer intergroup. J. Clin. Oncol. 27 (9), 1419–1425.

Burger, R.A., Brady, M.F., Bookman, M.A., Fleming, G.F., Monk, B.J., Huang, H., et al., 2011. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N. Engl. J. Med. 365 (26), 2473–2483.

Burger, R.A., Enserro, D., Tewari, K.S., Brady, M.F., Bookman, M.A., Fleming, G.F., et al., 2018. Final overall survival (OS) analysis of an international randomized trial evaluating bevacizumab (BEV) in the primary treatment of advanced ovarian cancer: a NRG oncology/gynecologic oncology group (GOG) study. J. Clin. Oncol. 36 (Suppl. 15) 5517-5517.

Cervantes-Ruiperez, A., Hoskins, P., Vergote, I., Eisenhauer, E.A., Ghatage, P., Carey, M., et al., 2013. Final results of OV16, a phase III randomized study of sequential cisplatin-topotecan and carboplatin-paclitaxel (CP) versus CP in first-line chemotherapy for advanced epithelial ovarian cancer (EOC): a GCIG study of NCIC CTG, EORTC-GCG, and GEICO. J. Clin. Oncol. 31 (Suppl_15) 5502-5502.

Chan, J.K., Brady, M.F., Penson, R.T., Huang, H., Birrer, M.J., Walker, J.L., et al., 2016. Weekly vs. Every-3-Week paclitaxel and carboplatin for ovarian cancer. N. Engl. J. Med. 374 (8), 738–748.

Clamp, A.R., McNeish, I., Dean, A., Gallardo, D., Kim, J.W.-, O'Donnell, D., et al., 2017. ICON 8: a GCIG phase III randomised trial evaluating weekly dose- dense chemotherapy integration in first-line epithelial ovarian/ fallopian tube/ primary peritoneal carcinoma (EOC) treatment: results of primary progression- free survival (PFS) analysis. Ann. Oncol. 28 (Suppl. 25), v605–v649.

Disis, M.L., Patel, M.R., Pant, S., Hamilton, E.P., Lockhart, A.C., Kelly, K., et al., 2016. Avelumab (MSB0010718C; anti-PD-L1) in patients with recurrent/refractory ovarian cancer from the JAVELIN solid tumor phase Ib trial: safety and clinical activity. J. Clin. Oncol. 34 (Suppl_15) 5533-5533.

du Bois, A., Floquet, A., Kim, J.W., Rau, J., del Campo, J.M., Friedlander, M., et al., 2014. Incorporation of pazopanib in maintenance therapy of ovarian cancer. J. Clin. Oncol. 32 (30), 3374–3382.

du Bois, A., Herrstedt, J., Hardy-Bessard, A.C., Muller, H.H., Harter, P., Kristensen, G., et al., 2010. Phase III trial of carboplatin plus paclitaxel with or without gemcitabine in first-line treatment of epithelial ovarian cancer. J. Clin. Oncol. 28 (27), 4162–4169.

du Bois, A., Kristensen, G., Ray-Coquard, I., Reuss, A., Pignata, S., Colombo, N., et al., 2016. Standard first-line chemotherapy with or without nintedanib for advanced ovarian cancer (AGO-OVAR 12): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet Oncol. 17 (1), 78–89.

du Bois, A., Luck, H.J., Meier, W., Adams, H.P., Mobus, V., Costa, S., et al., 2003. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. J. Natl. Cancer Inst. 95 (17), 1320–1329.

du Bois, A., Quinn, M., Thigpen, T., Vermorken, J., Avall-Lundqvist, E., Bookman, M., et al., 2005. 2004 consensus statements on the management of ovarian cancer: final document of the 3rd International Gynecologic Cancer Intergroup Ovarian Cancer Consensus Conference (GCIG OCCC 2004). Ann. Oncol. 16 (Suppl. 8), viii7–viii12.

du Bois, A., Weber, B., Rochon, J., Meier, W., Goupil, A., Olbricht, S., et al., 2006. Addition of epirubicin as a third drug to carboplatin-paclitaxel in first-line treatment of advanced ovarian cancer: a prospectively randomized gynecologic cancer intergroup trial by the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group and the Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens. J. Clin. Oncol. 24 (7), 1127–1135.

Fagotti, A., Vizzielli, G., Ferrandina, G., Fanfani, F., Gallotta, V., Chiantera, V., et al., 2018. Survival analyses from a randomized trial of primary debulking surgery versus neoadjuvant chemotherapy for advanced epithelial ovarian cancer with high tumor load (SCORPION trial). J. Clin. Oncol. 36 (Suppl_15) 5516-5516.

Hamanishi, J., Mandai, M., Ikeda, T., Minami, M., Kawaguchi, A., Murayama, T., et al., 2015. Safety and antitumor activity of Anti-PD-1 antibody, nivolumab, in patients with platinum-resistant ovarian cancer. J. Clin. Oncol. 33 (34), 4015–4022.

Harter, P., Reuss, A., Sehouli, J., Chiva, L., du Bois, A., 2017. Brief report about the role of hyperthermic intraperitoneal chemotherapy in a prospective randomized phase 3 study in recurrent ovarian cancer From spiliotis et al. Int. J. Gynecol. Cancer 27, 246–247 (Dann et al.).

Katsumata, N., Yasuda, M., Isonishi, S., Takahashi, F., Michimae, H., Kimura, E., et al., 2013. Long-term results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (JGOG 3016): a randomised, controlled, open-label trial. Lancet Oncol. 14 (10), 1020–1026.

Kehoe, S., Hook, J., Nankivell, M., Jayson, G.C., Kitchener, H., Lopes, T., et al., 2015. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. Lancet 386 (9990), 249–257.

Konstantinopoulos, P.A., Waggoner, S.E., Vidal, G.A., Mita, M.M., Fleming, G.F., Holloway, R.W., et al., 2018. TOPACIO/Keynote-162 (NCT02657889): a phase 1/2 study of niraparib + pembrolizumab in patients (pts) with advanced triple-negative breast cancer or recurrent ovarian cancer (ROC)—results from ROC cohort. J. Clin. Oncol. 36 (Suppl_15) 106-106.

Lim, M.C., Chang, S.-J., Yoo, H.J., Nam, B.-H., Bristow, R., Park, S.-Y., 2017. Randomized trial of hyperthermic intraperitoneal chemotherapy (HIPEC) in women with primary advanced peritoneal, ovarian, and tubal cancer. J. Clin. Oncol. 35 (Suppl_15) 5520-

5520.
Lindemann, K., Christensen, R.D., Vergote, I., Stuart, G., Izquierdo, M.A., Kaern, J., et al., 2012. First-line treatment of advanced ovarian cancer with paclitaxel/carboplatin with or without epirubicin (TEC versus TC)–a gynecologic cancer intergroup study of the NSGO, EORTC GCG and NCIC CTG. Ann. Oncol. 23 (10), 2613–2619.
Mahner, S., Heitz, F., Burges, A., Reuss, A., Kraemer, B., Schmalfeldt, B., et al., 2017. TRUST: trial of radical upfront surgical therapy in advanced ovarian cancer (ENGOT ov33 / AGO-OVAR OP7). J. Clin. Oncol. 35 (Suppl_15) TPS5602-TPS5602.
Markman, M., Bundy, B.N., Alberts, D.S., Fowler, J.M., Clark-Pearson, D.L., Carson, L.F., et al., 2001. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. J. Clin. Oncol. 19 (4), 1001–1007.
Marth, C., Wieser, V., Tsibulak, I., Zeimet, A.G., 2019. Immunotherapy in ovarian cancer: fake news or the real deal? Int. J. Gynecol. Cancer 29 (January (1)), 201–211 2019.
McGuire, W.P., Hoskins, W.J., Brady, M.F., Kucera, P.R., Partridge, E.E., Look, K.Y., et al., 1996. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N. Engl. J. Med. 334 (1), 1–6.
Mirza, M.R., Monk, B.J., Herrstedt, J., Oza, A.M., Mahner, S., Redondo, A., et al., 2016. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N. Engl. J. Med. 375 (22), 2154–2164.
Moore, K., Colombo, N., Scambia, G., Kim, B.G., Oaknin, A., Friedlander, M., et al., 2018. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N. Engl. J. Med.
Onda, T., Satoh, T., Saito, T., Kasamatsu, T., Nakanishi, T., Takehara, K., et al., 2018. Comparison of survival between upfront primary debulking surgery versus neoadjuvant chemotherapy for stage III/IV ovarian, tubal and peritoneal cancers in phase III randomized trial: JCOG0602. J. Clin. Oncol. 36 (Suppl_15) 5500-5500.
Ozols, R.F., Bundy, B.N., Greer, B.E., Fowler, J.M., Clarke-Pearson, D., Burger, R.A., et al., 2003. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. J. Clin. Oncol. 21 (17), 3194–3200.
Perren, T.J., Swart, A.M., Pfisterer, J., Ledermann, J.A., Pujade-Lauraine, E., Kristensen, G., et al., 2011. A phase 3 trial of bevacizumab in ovarian cancer. N. Engl. J. Med. 365 (26), 2484–2496.
Pfisterer, J., Weber, B., Reuss, A., Kimmig, R., du Bois, A., Wagner, U., et al., 2006. Randomized phase III trial of topotecan following carboplatin and paclitaxel in first-line treatment of advanced ovarian cancer: a gynecologic cancer intergroup trial of the AGO-OVAR and GINECO. J. Natl. Cancer Inst. 98 (15), 1036–1045.
Piccart, M.J., Bertelsen, K., James, K., Cassidy, J., Mangioni, C., Simonsen, E., et al., 2000. Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. J. Natl. Cancer Inst. 92 (9), 699–708.
Pignata, S., Scambia, G., Ferrandina, G., Savarese, A., Sorio, R., Breda, E., et al., 2011. Carboplatin plus paclitaxel versus carboplatin plus pegylated liposomal doxorubicin as first-line treatment for patients with ovarian cancer: the MITO-2 randomized phase III trial. J. Clin. Oncol. 29 (27), 3628–3635.
Pignata, S., Scambia, G., Katsaros, D., Gallo, C., Pujade-Lauraine, E., De Placido, S., et al., 2014. Carboplatin plus paclitaxel once a week versus every 3 weeks in patients with advanced ovarian cancer (MITO-7): a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol. 15 (4), 396–405.
Rose, P.G., Nerenstone, S., Brady, M.F., Clarke-Pearson, D., Olt, G., Rubin, S.C., et al., 2004. Secondary surgical cytoreduction for advanced ovarian carcinoma. N. Engl. J. Med. 351 (24), 2489–2497.
Spiliotis, J., Halkia, E., Lianos, E., Kalantzi, N., Grivas, A., Efstathiou, E., Giassas, S., 2015. Cytoreductive surgery and HIPEC in recurrent epithelial ovarian cancer: a prospective randomized phase III study. Ann. Surg. Oncol. 22 (5), 1570–1575.
van der Burg, M.E., van Lent, M., Buyse, M., Kobierska, A., Colombo, N., Favalli, G., et al., 1995. The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. Gynecological Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer. N. Engl. J. Med. 332 (10), 629–634.
van Driel, W.J., Koole, S.N., Sikorska, K., Schagen van Leeuwen, J.H., Schreuder, H.W.R., Hermans, R.H.M., et al., 2018. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. N. Engl. J. Med. 378 (3), 230–240.
Vasey, P.A., Jayson, G.C., Gordon, A., Gabra, H., Coleman, R., Atkinson, R., et al., 2004. Phase III randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first-line chemotherapy for ovarian carcinoma. J. Natl. Cancer Inst. 96 (22), 1682–1691.
Vergote, I., Amant, F., Kristensen, G., Ehlen, T., Reed, N.S., Casado, A., 2011. Primary surgery or neoadjuvant chemotherapy followed by interval debulking surgery in advanced ovarian cancer. Eur. J. Cancer 47 (Suppl. 3), S88–92.
Vergote, I., Hanker, L.C., Floquet, A., Rau, J., Kim, J.-W., Izquierdo, E.O., et al., 2018. AGO-OVAR 16: a phase III study to evaluate the efficacy and safety of pazopanib (PZ) monotherapy versus placebo in women who have not progressed after first line chemotherapy for epithelial ovarian, fallopian tube, or primary peritoneal cancer—overall survival (OS) results. J. Clin. Oncol. 36 (Suppl_15) 5518-5518.
Vergote, I., Scambia, G., O'Malley, D.M., Calster, B.V., Park, S.-Y., Campo, J.M., et al., 2016. TRINOVA-3/ENGOT-ov-2/GOG-3001: a randomised, double-blind phase 3 study of trebananib plus carboplatin/paclitaxel as first line treatment in advanced ovarian cancer. Int. J. Gynecol. Cancer 26 (Suppl. 3), 13.
Vergote, I., Tropé, C.G., Amant, F., Kristensen, G.B., Ehlen, T., Johnson, N., et al., 2010. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N. Engl. J. Med. 363 (10), 943–953.
Walker, J., Brady, M.F., DiSilvestro, P.A., Fujiwara, K., Alberts, D., Zheng, W., et al., 2016. A phase III trial of bevacizumab with IV versus IP chemotherapy for ovarian, fallopian tube, and peritoneal carcinoma: an NRG Oncology Study. Gynecol. Oncol. 141, 208.

Irina Tsibulak was born in Ukraine and graduated in Medicine at the Medical University of Innsbruck, Austria, in 2015. In 2015–2016 she was a surgical resident at the Department of Visceral, Transplant and Thoracic Surgery in Innsbruck. From 2016 she is a resident doctor at the Department of Obstetrics and Gynecology of Innsbruck University Hospital and is involved in clinical research on gynecologic oncology.

Alain G. Zeimet was born in Luxembourg and graduated in Medicine at the University of Innsbruck, Austria, in 1990. From 1988–1989 he was a scientific fellow of Prof. P.M. Martin, University of Aix-en-Provence/Marseille; Institute of Experimental Cancer Research, Department of Steroid Receptor Research (CRNS-Unit), Marseille. He completed his Obstetrics and Gynecology residency at the Department of Obstetrics and Gynecology of Innsbruck University Hospital in 1997 and he qualified as professor in 1998 (PhD). Since 2002 Dr. Zeimet is the Vice Head of the Department of Obstetrics and Gynecology and the Head of the Gynecologic Oncology unit at the Medical University of Innsbruck. His clinical and research interests focus the field of ovarian and endometrial cancer. Dr. Zeimet authored more than 180 scientific research articles. He was the president of the Austrian Association for Gynecologic Oncology from 2005 to 2007 and in a second term from 2013 – 2015. He is a member of numerous national and international scientific organizations and guidelines committees for gynecologic cancers.

Christian Marth is Head and Professor of the Department of Obstetrics and Gynecology at Innsbruck Medical University in Austria. After graduating in medicine from Innsbruck Medical University in 1985, he specialized in obstetrics and gynecology in Innsbruck, becoming senior physician in 1990. A year later he became a specialist in obstetrics and gynaecology, and completed his habilitation. In 1996, Christian Marth moved to The Norwegian Radiumhospital, Oslo, where he was senior physician at the Department of Gynecologic Oncology. After being made Associate Professor at the University of Innsbruck in 1997, he returned to Innsbruck in 1998 as Head of the Department of Obstetrics and Gynecology. Christian Marth has been President of the Austrian Association for Gynecologic Oncology (2001–2003, 2013–2016), Chair of the Ovarian Committee of Gynecological Cancer Intergroup (2007–2012), a Council member of the European Society of Gynecologic Oncology ESGO (2009–2016), President of the Austrian Association of Obstetrics and Gynecology (2011–2013), and Chair of the European Network of Gynaecological Oncological Trial Groups (2014–2016). Currently, he is the President of the Austrian Study Center for Gynecologic Oncology (since 2002), and Vice-President of the Austrian Breast and Colorectal Study Group (since 2006). Christian Marth has also been the author or co-author of more than 400 peer-reviewed scientific articles, and has received 13 national and international awards.