TABLE 1. Comparison between small cell carcinomas, squamous carcinomas, and adenocarcinomas of the uterine cervix (McCusker et al,[4,10–13] Wistuba et al,[4,10–13] Hirai et al,[4,10–13] Scotto et al,[4,10–13] Tornesello et al[4,10–13])

Cervical Carcinomas	Small Cell Carcinoma	Squamous Cell Carcinoma	Endocervical Adenocarcinoma, Usual Type
Incidence, % of cases	2–5	75	20–25
Mean age at diagnosis, yrs	49	52	46
Morphology	Small or spindle cells	Polygonal or spindle cells	Columnar cells
	Scant cytoplasm	+/− Abundant eosinophilic cytoplasm	Abundant cytoplasm
	Hyperchromatic and smudged nuclei	Atypical, large nuclei	Scant intracellular mucin
	Nuclear molding	Coarse, granular chromatin	Large nuclei
	No nucleoli	Mitoses	Nucleoli
	Many mitosis+++	Masses with central keratin formation and necrosis	Mitoses
	Necrosis		Apoptotic bodies
	No gland		Gland formation, papillary and solid pattern
	Rosettes and ribbons		
	Lymphovascular invasion 60%–90%	Lymphovascular invasion 25%	Lymphovascular invasion
Immunoprofile	Pankeratin +	Pankeratin +++	Pankeratin +++
	CK7 −/+	CK7 −/+, CK14 +, CK5/6 +	CK7 +++
	Neuroendocrine markers 30 − 50% + for at least one	Neuroendocrine markers Usually −	Neuroendocrine markers Usually −
	P16 +++	P16 +++	P16 +++
	TTF1 may be +	TTF1 −	TTF1 −
	P 63 − (+/−30%)	P63 +++	P63 usually −
	CEA −	CEA −	CEA cytoplasmic +++
	ER and PR usually −	ER and PR usually +	ER and PR usually −
Molecular biology	HPV-18 (53%) >> HPV-16	HPV-16 > HPV-18 (15%)	HPV-18 (50%) > HPV-16
	TP53 mutation, 47%	*TP53* mutation, 5.9% (codon 249)	*TP53* mutation, 13.3% (codon 282)
	Deletion of 3p (47%)	Deletion of 3p (85%)	Deletion 3p
	Deletion 9p21 (43%)	Deletion 9p21 (11%)	Deletion 2q (25%)
	No *KRAS* mutation	Gain 20q (>50%)	Deletion 5p (38%)
		EGFR amplification (10%)	No *EGFR* amplification
		KRAS mutations rares	No *KRAS* mutation

(Continued on next page)

TABLE 1. *(Continued)*

Cervical Carcinomas	Small Cell Carcinoma	Squamous Cell Carcinoma	Endocervical Adenocarcinoma, Usual Type
Behavior	Very aggressive Positive lymph nodes > 50%	16.9% stage IB1 at diagnosis Positive lymph nodes (15%–20% stage IB, 50% stage III)	26.7% stage IB1 at diagnosis Positive lymph nodes, 20%
	Distant metastases lung, liver, bone, brain	Pelvic recurrences Distant metastases rares (lung, 6%)	Metastases ovary (5%), intra-abdominal, para-aortic lymph nodes, adrenal glands, lung, pleura

CEA, Carcinoembryonic antigen; CK, cytokeratin; ER, estrogen receptors; HPV, human papillomavirus; PR, progesterone receptors; TTF-1, thyroid transcription factor −1.

addition, the Japanese Society of Obstetrics and Gynecology has reported that the incidence of SCCC was approximately 1%, and 0.6% in Korea[15] from 1993 to 2002. The incidence of SCCC in extrapulmonary small cell cancer was reported as 9.9%,[16] 18.0%,[17] and 4.7%[18] in each article. The median age at diagnosis for patients with SCCC was approximately 45 years,[19–21] similar to SC or AC. The stage distribution of SCCC is similar to SC and AC, mostly early stage at diagnosis, although in one study, lymph node involvement is more common in SCCC: 50% compared to 18% in SC.[1]

PATHOLOGY

From a diagnostic point of view, there may be problems distinguishing SCCC from other neoplasms, and in confirming a cervical origin. This is important, as management is critically dependent on the correct histologic diagnosis. Cervical neuroendocrine carcinomas (NECs) are subdivided into small cell NEC and large cell NEC and are usually characterized by immunohistochemical expression of pancytokeratin (AE1/AE3) and neuroendocrine markers (chromogranin, synaptophysin, and CD56). They are usually negative for P63, although some positive cases have been described,[22] whereas squamous cell carcinomas are P63 positive and chromogranin negative.[23] However, a significant proportion of cervical NECs may be negative for broad-spectrum cytokeratins and some of the commonly used neuroendocrine markers. Thyroid transcription factor 1 positivity is extremely common and may be a useful marker of an NEC, but this positivity is of no value in exclusion of a pulmonary primary.[22] p16 is almost always positive in cervical NECs, possibly owing to an association with oncogenic human papillomavirus, although other mechanisms of expression are also possible.[22] CK20 and neurofilament positivity in some cervical NECs is in keeping with a Merkel cell immunophenotype, similar to that described in small cell NECs in other organs[22].

MOLECULAR PATTERN

Several studies have described a spectrum of molecular changes involved in the pathogenesis of squamous cell carcinoma, the most frequent histologic type of cervical cancer. However, other than human papillomavirus (HPV) sequences, no data about genetic changes present in endocrine tumors of the uterine cervix have been reported. The morphologic and clinical features of the endocrine tumors of the uterine cervix are similar to those occurring in the lung, and a similar histologic classification has been adopted. In 1999, Wistuba et al[10] described the distinct molecular changes that are present in neuroendocrine tumors of the uterine cervix. They demonstrated a high incidence of oncogenic HPV sequences (especially HPV type 18) and TP53 gene abnormalities, relatively small deletions of chromosome 3p regions, and occasional 9p21 deletions. Thus, these tumors share some changes present in the neuroendocrine tumors of the lung (TP53 gene abnormalities and 9p21 allelic loss) as well those in squamous carcinomas of the cervix (oncogenic HPV

TABLE 2. Comparison of survival by stage in patients with small cell carcinoma of the cervix

Author	Stage							
	IB1	IB2	IIA	IIB	IIIA	IIIB	IVA	IVB
Cohen et al[20]	36.8% (35)				8.9% (53)			
Lee et al[25]		46%–53% (48)						
Wang et al[23]	51.1% (104)			50.4% (42)		13.0% (9)		6.1% (24)
Kuji et al[31]	63% (17)	67% (10)		30% (10)		29% (7)		25% (6)

Five-year survival rate (number of patients).
For Kuji et al, 4-year survival rate (number of patients).

sequences and localized 3p deletions). However, their overall genetic profile is distinct and different from that of the other 2 tumor types.[10]

INITIAL TREATMENT

Management algorithm for NEC of the cervix has been published as a Society of Gynecologic Oncology clinical document.[24] As shown in Figure 1, radical surgery is recommended for early-stage disease either primarily or after neoadjuvant chemotherapy. For patients with advanced-stage disease, chemoradiation or systemic chemotherapy is suggested.

A retrospective study in 68 patients with stage IB1 to stage IIA disease reported by Lee et al[25] suggested that radical hysterectomy followed by adjuvant chemotherapy might be sufficient, as the patients who received CCRT did not seem to have a better outcome.[25] However, in a report from Tian et al[26] of 96 women with stage IB1-IIA SCCC adjuvant chemotherapy after radical hysterectomy did not appear to improve the prognosis. Similar findings were reported by Cohen et al; postoperative adjuvant chemotherapy on 135 patients with stage I to stage IIA disease in an analysis of 188 cases of stage I to stage IV disease did not seem to influence outcome.[20] However, Kuji et al demonstrated significantly better progression-free and overall survival for the patients with stage IB1 to IIB disease who received chemotherapy after radical surgery compared with the patients who did not receive chemotherapy. Therefore, the benefit of adding chemotherapy after radical hysterectomy is controversial at present. It is possible that the findings of no benefit by chemotherapy are due to poor activity of the regimens used. It has recently been reported that CCRT using a regimen consisting of vincristine, doxorubicin, and cyclophosphamide alternating with etoposide and cisplatin (EP) was a useful postoperative chemotherapy regimen in early-stage disease, although the number of cases reported was small.[27]

In advanced disease, stages IIB to IVA, Cohen et al[20] reported an improvement in prognosis in patients who were treated with chemotherapy. A combined modality approach, adding CCRT to chemotherapy, was reported by Wang et al.[28] The addition of at least 5 cycles of EP significantly improved the prognosis of 56 patients with stage IIB to IVB disease in an analysis of 179 cases of stage I to stage IV disease.[28] At present, it seems that chemotherapy may be effective in advanced stages of SCCC.

The EP regimen was used in approximately half of the cases reported by Lee et al, including the neoadjuvant setting. Other regimens used were paclitaxel and cisplatin, paclitaxel and carboplatin, and vincristine, cisplatin, and bleomycin.[25] Cohen et al used EP in 51.9% of their cases, and other regimens including cisplatin combination or cisplatin alone were used in 33.3%.[20] Wang et al reported that EP was used in 49%, and other regimens including cisplatin were used in 38%.[28] Etoposide and cisplatin (EP) is the most frequently used regimen, as used in the treatment of small cell lung cancer (SCLC),[29] but prospective trials in SCCC are lacking.

The typical EP regimen was proposed for advanced small cell carcinoma of the lung. Usually, cisplatin at 60 to

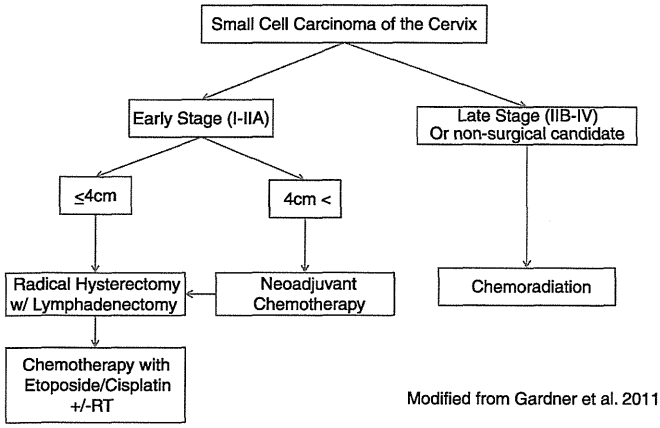

FIGURE 1. Management algorithm of SCCC (modified from Gardner et al.[24]).

80 mg/m^2 is given intravenously on day 1 and etoposide at 80 to 120 mg/m^2 IV on days 1 to 3 every 21 to 28 days.[6,8,9]

Prognostic Factors

The greatest differences in survival between SCCC and SC or AC were seen in patients with early-stage and node-negative disease (Table 2).[3] The 5-year disease-specific survival rates of patients with stage I to stage IIA SCCC (n = 135), IIB to IVA (n = 45), and IVB (n = 8) disease were 36.8%, 9.8%, and 0%, respectively.[20] The median overall survival for patients with early-stage disease (IA1-IB2 [n = 11]) was 31.2 months, and the median overall survival for patients with advanced-stage disease (IIB-IV [n = 6]) was 6.4 months.[19] The most recently reported 5-year cancer-specific survival rates for patients with stage I (n = 104), stage II (n = 42), stage III (n = 9), and stage IV (n = 24) disease were 51.5%, 50.4%, 13.0%, and 6.1%, respectively.[28]

Regarding the 5-year overall survival rate, Lee et al reported that the rate was 55% in patients with IB1 disease (n = 43) and 32% in patients with stage IB2 to IIA disease (n= 25).[25] Cohen et al[20] reported 36.8% in patients with stage I to stage IIA (n = 135), 9.8% in patients with stage IIB to IVA disease (n = 45), and 0% in patients with stage IVB disease (n = 8). Wang et al[28] reported 50% in patients with stage IA disease (n = 3), 54% in those with stage IB1 disease (n = 69), 46% in patients with stage IB2 disease (n = 32), 53% in patients with stage IIA (n = 19), 49% in patients with stage IIB disease (n = 23), 13% in patients with stage III disease (n = 9), 33% in patients with stage IVA disease (n = 3), and 0% in patients with stage IVB disease (n = 21).

The only independent prognostic factor Lee JM et al found was stage (IB1 vs IB2-IIA).[25] Stage (IA-IIA vs IIB-IVA vs IVB), radical hysterectomy, and the use chemotherapy (including CCRT), were the 3 independent prognostic factors Cohen et al[20] found. Wang et al[28] reported that 2 factors, stage (IA-IIA vs IIB-IV) and lymph node metastasis, were prognostic. In an analysis of 290 cases in the SEER database, Chen et al[3] identified 3 independent prognostic factors: age, stage, and race. Stage is the only prognostic factor common to all these studies. Liao et al[30] reported a large retrospective study with 293 patients, and the prognostic factors were International Federation of Gynecology and Obstetrics stage, tumor mass size, lymph node metastasis, depth of stromal invasion, and chromogranin A positivity by univariate analysis, and International Federation of Gynecology and Obstetrics stage, tumor size, and chromogranin A positivity were the prognostic factors by multivariate analysis. Kuji et al[31] showed significantly better of progression-free survival by addition of chemotherapy after radical surgery.

In addition, it is unclear if patients with SCCC benefit from the use of prophylactic cranial radiation after primary treatment in the same way as those with pulmonary small cell carcinomas. Several studies suggest that the rate of brain metastases with extrapulmonary small cell is much lower than seen in pulmonary small cell. Hence, several authors suggest that prophylactic cranial radiation could be omitted for these patients.[21,32,33]

METASTATIC DISEASE AND RELAPSE

The prognosis of patients with stage IVB disease with distant metastasis is very poor. None of the 29 patients with stage IVB disease survived 5 years.[20,28] There is no information on the results of treatment of recurrent disease. It is important that information on these women is collected. There is an urgent need to develop new and better treatments for SCCC. Kuji et al reported that 21 patients among 52 patients with SCCC had recurrence, and 67% of the initial recurrent sites were hematogenous or hematogenous and lymphogenous. Only 10% was local recurrence, suggesting the importance of chemotherapy in this patient population.

CURRENT STATUS AND FUTURE RESEARCH DIRECTIONS

As discussed in this review article, no standard treatment guideline has been established for SCCC because there has been no prospective randomized study. Therefore, the most important thing is to conduct a randomized phase 2/3 trial under the GCIG platform. The questions to be asked in the trial would include the optimal treatment strategy for early-stage SCCC and optimal chemotherapy regimen, more potent or less toxic regimen compared with EP. Target agents also should be investigated.

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Neoadjuvant chemotherapy in advanced ovarian cancer: latest results and place in therapy

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Neoadjuvant chemotherapy in advanced ovarian cancer: latest results and place in therapy

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Abstract: Approximately 70% of women with epithelial ovarian cancer (EOC) are diagnosed with advanced stage disease, which is associated with high morbidity and mortality. The standard approach to treating patients with advanced EOC remains primary debulking surgery (PDS) followed by chemotherapy. EOC is one of the most sensitive of all solid tumors to cytotoxic drugs, with over 80% of women showing a response to standard chemotherapy combined with taxane and platinum. Furthermore, residual disease is a major prognostic factor for survival. On the basis of the clinical features, neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) is considered to be an alternative treatment option to standard treatment in patients unable to undergo complete resection during PDS. Noninferiority of NACT-IDS to PDS has been demonstrated in some randomized controlled trials and meta-analyses. NACT would also lead to improved quality of life (QOL) of patients, however there are still problems to be solved in the treatment strategy. The uncertainty of perioperative visual assessment of tumor dissemination after NACT has been reported. In addition, several papers have shown the possibility that NACT induces platinum resistance. Furthermore, a notable risk associated with NACT is that patients with significant side effects and refractory disease will lose the opportunity for debulking surgery. Appropriate selection of the patient cohort for NACT is an important issue. Bevacizumab (Bev) is active in patients with advanced EOC. However, the use of Bev is not recommended in the neoadjuvant setting. Bev has a specific adverse event profile that needs to be considered, especially for surgical management, such as gastrointestinal perforation, hemorrhage, and thromboembolic events. NACT could be an alternative treatment option in patients with stage III or IV EOC. However, further studies are needed to clarify the precise role of NACT in the management of advanced EOC.

Keywords: advanced ovarian cancer, interval debulking surgery, neoadjuvant chemotherapy

Introduction

Epithelial ovarian cancer (EOC) is the leading cause of death in women with gynecological malignancy [Ferlay *et al.* 2010]. The estimated annual incidence of EOC is 225,500 with an estimated 140,200 deaths worldwide in 2008, consisting of 3.7% of all female cancers and 4.2% of cancer deaths [World Health Organization, 2011]. Due to inadequate screening tools and a lack of early clinical symptoms, approximately 70% of women with EOC are diagnosed with advanced stage of disease, which is associated with high morbidity and mortality [Cannistra, 2004; Heintz *et al.* 2006; Jemal *et al.* 2010]. Currently, standard primary therapy for patients with advanced EOC is primary debulking surgery (PDS) aiming to remove all visible tumor tissue, followed by adjuvant chemotherapy (ACT) with paclitaxel and carboplatin [Du Bois *et al.* 2005; Du Bois and Pfisterer, 2005; Pignata *et al.* 2011]. Despite treatment with this strategy, the majority of these patients develop a relapse within the first 5 years after initial diagnosis and only 20–25% of cases are cured. Furthermore, 5-year survival rate of patients with advanced EOC has not seen a clear improvement in the last decade.

Recently, interval debulking surgery (IDS) after a short course of neoadjuvant chemotherapy

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(NACT), usually three cycles of chemotherapy, has become a possible alternative treatment option to standard treatment in patients unable to undergo complete resection during PDS. Several randomized trials have shown that, although progression-free survival (PFS) and overall survival (OS) rates in patients given NACT-IDS were not different from those of patients undergoing PDS, patients who received NACT had significantly lower adverse effect and mortality rates after IDS than patients undergoing PDS [Van Der Burg *et al.* 1995; Rose *et al.* 2004; Vergote *et al.* 2010]. Therefore, the significance of NACT-IDS has been further appreciated. In this review, we describe the latest knowledge relating to the use of NACT-IDS to treat advanced EOC.

The place of NACT in the treatment of advanced EOC

Residual disease at the end of surgery is a major prognostic factor for survival [Winter *et al.* 2007], justifying extensive cytoreductive surgery. Gynecologic oncologists perform a resection of disseminated disease by resecting the peritoneum and other organs such as the intestinal tract, liver and spleen, in addition to staging laparotomy. Over the last decade, the goal of advanced EOC debulking surgery has changed from residual tumor less than 1 cm to no macroscopic residual tumor both in PDS and IDS [Hoskins *et al.* 1992, 1994; Eisenkop *et al.* 1998; Vergote *et al.* 1998, 2010, 2011a; Bristow *et al.* 2002; Aletti *et al.* 2006; Chi *et al.* 2006, 2009; Winter *et al.* 2007; Du Bois *et al.* 2009]. However, complete resection of the tumor is often difficult for patients with massively disseminated tumors.

EOC is one of the most sensitive of all solid tumors to cytotoxic drugs, with over 80% of women showing a response to standard chemotherapy combining taxane and platinum. Even if preoperative diagnostic imaging shows massive ascites and diffuse dissemination, these show a dramatic disappearance at IDS after NACT. Based on these clinical characteristics, NACT has been proposed to reduce the burden of disease in patients with bulky disease [Jacob *et al.* 1991; Schwartz *et al.* 1994; Vergote *et al.* 1998, 2000]. While the standard approach to treating patients with advanced EOC remains PDS followed by platinum-based chemotherapy, NACT-IDS is a treatment approach gaining increasing popularity [Schwartz, 2008, 2009; Fago-Olsen *et al.* 2014].

NACT is defined as the chemotherapy performed prior to cytoreductive surgery. In recent years, NACT-IDS has gained credibility as a valid therapeutic strategy especially for patients with stage IV unresectable bulky tumors or poor general condition [Cannistra, 2004; Rauh-Hain *et al.* 2012]. NACT setting treatment is now expected to become a standard treatment or one of the effective treatment options for advanced EOC.

Clinical evidence of NACT

To date, there have been some prospective, randomized studies examining the utility of NACT-IDS in patients with advanced EOC (Table 1).

A randomized phase III trial conducted by the European Organization for the Research and Treatment of Cancer (EORTC) evaluated the benefit of IDS after suboptimal primary debulking by comparing 140 patients who received three cycles of cisplatin and cyclophosphamide chemotherapy followed by IDS and three additional cycles of ACT with 138 similar patients receiving the same chemotherapy regimen without IDS. The IDS group had a statistically significant advantage in median survival time (26 months) compared with patients not undergoing IDS (20 months) [Van Der Burg *et al.* 1995].

Similarly, in a randomized phase III trial conducted by the Gynecologic Oncology Group (GOG), 550 patients with stage III and IV EOC left with residual disease greater than 1 cm following an initial attempt at PDS [Rose *et al.* 2004]. All patients received three cycles of initial chemotherapy with cisplatin and paclitaxel followed by response evaluation. Patients whose disease had not progressed during the treatment interval were randomly assigned to IDS plus three additional cycles of ACT or additional chemotherapy alone. In contrast to the EORTC trial, the likelihood of PFS in the group assigned to IDS plus chemotherapy was not significantly different compared with the chemotherapy alone group [hazard ratio (HR) 1.07, 95% confidence interval (CI) 0.87–1.31, $p = 0.54$]; there was also no significant difference in relative risk of death for patients undergoing interval surgery (relative risk 0.99, 95% CI 0.79–1.24, $p = 0.92$).

A randomized trial was recently performed by EORTC and the National Cancer Institute of Canada (NCIC) comparing PDS with NACT-IDS [Vergote *et al.* 2010]. In this trial, 718 patients

Table 1. Characteristics of randomized control trials.

Author, year	*n* (eligible)	FIGO stage	Residual disease status	Interventions	Median OS, months (significance)
Van Der Burg, 1995 (EORTC trial)	278	IIB–IV	> 1 cm	Arm 1: IDS after three cycles of triweekly CPA and CDDP followed by three more cycles of the same regimen Arm 2: PDS followed by six cycles of the same regimen of chemotherapy	26.0 20.0 [p = 0.01]
Rose, 2004 [GOG trial]	424	III–IV	> 1 cm	Arm 1: IDS after three cycles of triweekly TP, followed by three more cycles of the same regimen Arm 2: PDS followed by six cycles of the same regimen of chemotherapy	33.9 33.7 [NS]
Vergote, 2010 (EORTC/NCIC trial)	670	IIIC–IV	> 1 cm	Arm 1: IDS after three cycles of platinum-based NACT, followed by three more cycles of ACT Arm 2: PDS followed by at least six courses of platinum-based chemotherapy	29.0 30.0 [NS]

ACT, adjuvant chemotherapy; CDDP, cisplatin; CPA, cyclofosfamide; EORTC, European Organization for the Research and Treatment of Cancer; GOG, Gynecologic Oncology Group; IDS, interval debulking surgery; NACT, neoadjuvant chemotherapy; NCIC, National Cancer Institute of Canada; NS, not significant; OS, overall survival; PDS, primary debulking surgery; TP, paclitaxel/cisplatin.

with epithelial ovarian, fallopian tube or primary peritoneal carcinoma were enrolled. All patients had International Federation of Gynecology and Obstetrics (FIGO) stage IIIC and IV disease and were randomly assigned to PDS followed by platinum-based chemotherapy (PDS group) or NACT followed by IDS (NACT group). The largest residual tumor was 1 cm or smaller (optimal surgery) after PDS in 41.6% of patients and after IDS in 80.6% of patients. Although PFS and OS were similar in both groups, postoperative infections, venous complications, fistula, hemorrhage and postoperative mortality tended to be higher after PDS. A noteworthy drop in OS was noted during the first 3 months after randomization as a result of postoperative mortality and delay of postoperative chemotherapy in patients undergoing PDS. Complete resection of all macroscopic disease (at PDS or IDS) was the strongest independent variable in predicting OS. The authors concluded that NACT-IDS was not inferior to PDS followed by chemotherapy as a treatment option for patients with bulky stage IIIC or IV EOC and complete resection of all macroscopic disease, whether performed as primary treatment or after NACT, remains the objective whenever cytoreductive surgery is performed.

Several other phase III trials are ongoing aiming to address the question of whether NACT before surgery could replace the primary surgery before ACT in terms of survival comparison (Table 2). The latest results of the trial run by the Royal College of Obstetricians and Gynecologists in the UK (CHORUS study) were presented at the 2013 American Society of Clinical Oncology annual meeting [Kehoe *et al.* 2013]. This trial was designed to demonstrate the noninferiority of NACT to PDS. A total of 552 patients with stage III/IV EOC were enrolled between 2004 and 2010. Of these, 276 had been randomly assigned to PDS followed by six cycles of platinum-based ACT and 274 had been randomly assigned to three cycles of platinum-based NACT followed by surgery and then three cycles of ACT. Baseline characteristics were well balanced. Median age was 65.5 years, median tumor size was 8 cm and 25% had stage IV disease. Median duration of follow up was 3 years. About 20% of patients in both arms had poor performance status (PS). Optimal debulking was possible in 16% of the PDS arm *versus* 40% of the NACT arm. Grade 3 or higher toxicity occurred in 48% and 40% in the NACT and PDS groups respectively, while postoperative complications of grade 3 or 4 occurred in 24% and 14% respectively. Fewer deaths within 28 days were reported with NACT: 14 (5.6%) deaths were noted in the PDS arm while 1 (0.5%) occurred in the NACT arm. Intention to treat analysis showed a median OS of

Table 2. Characteristics of ongoing randomized control trials.

Study	CHORUS	Kumar	JCOG0602
Identifier	NCT00075712	NCT00715286	UMIN000000523
Timing of randomization	Randomized at entry	Randomized at surgery	Randomized at entry
Number randomized (estimated)	150	180	300
Participants	Stage: III–IV Age < 18 Pelvic mass with extrapelvic metastases Serum CA125/CEA > 25	Stage: IIIc–IV (pleural effusion only) Age: 25–65 PS ECOG: 0–2 Cytology/biopsy positive	Stage: III–IV Age: 20–75 PS ECOG: 0–3 Cytology positive Serum CA125 > 200 U/ml and CEA <20 ng/ml
Interventions	Arm 1: PDS followed by six cycles of triweekly TC or CBDCA alone. Patients may undergo IDS after three courses of chemotherapy Arm 2: three courses of chemotherapy as in arm 1 followed by IDS, and three courses of ACT	Arm 1: PDS followed by ACT Arm 2: NACT followed by IDS	Arm 1: PDS followed by eight courses of triweekly TC. Patients may undergo IDS after four courses of chemotherapy Arm 2: four courses of chemotherapy as in arm 1 followed by IDS, and four courses of ACT
Outcomes of interest	OS, PFS QOL	Optimal debulking rate OS, DFS, QOL	OS, PFS Response rate, adverse effects, perioperative complications

ACT, adjuvant chemotherapy; CBDCA, carboplatin; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group;; IDS, interval debulking surgery; JCOG, Japan Clinical Oncology Group; NACT, neoadjuvant chemotherapy; OS, overall survival; PDS, primary debulking surgery; PFS, progression-free survival; PS, performance status; QOL, quality of life; TC, paclitaxel/carboplatin.

22.8 months and 24.5 months for PDS and NACT respectively (HR 0.87 in favor of NACT, 80% CI 0.76–0.98) and median PFS of 10.2 and 11.7 months respectively (HR 0.91, 80% CI 0.81–1.02) [Kehoe *et al.* 2013]. These results strengthened the evidence that NACT-IDS is not inferior to PDS.

The Japan Clinical Oncology Group in Japan (JCOG 0602) designed a similar trial (Table 2), with patients in the NAC arm having IDS (which is actually the first or primary surgery) before further chemotherapy, while patients in the other arm had conventional treatment (patients in the conventional arm may also have had IDS upon direction of the physician). To directly address the definite role of IDS, future studies should focus on a comparison of current conventional primary surgery with ACT *versus* NACT without any attempt to remove the bulk of tumors followed by IDS (which should be allowed only in this arm) and then by further chemotherapy. The appropriate number of cycles of NACT remains uncertain. The safety and efficacy of six cycles of paclitaxel/carboplatin (TC) therapy as NACT has been confirmed [Da Costa Miranda *et al.* 2014; Stoeckle *et al.* 2014]. However, the duration of the initial treatment will be longer when ACT is added after NACT-IDS [Milam *et al.* 2011]. Therefore, a study of the optimal number of cycles of NACT is necessary.

In a meta-analysis including articles between 1989 and 2005, a total of 835 patients with stage III and IV EOC treated with platinum-based NACT *in lieu* of PDS were evaluated with regard to OS and relative effect of multiple prognostic variables [Bristow and Chi, 2006]. In this study, median survival time was 24.5 months and optimal surgery occurred in 65% of patients. Median OS was positively correlated with platinum plus taxane chemotherapy and more recent year of publication, and negatively correlated with the proportion of stage IV disease. A prognosis improvement of 1.9 months was observed for every percentage of optimal cases increase 10%. However, shortened survival of 4.1 months was observed in each increased by one course of

NACT. The median survival time of the NACT group was equivalent to that of patients with PDS ended in suboptimal in GOG study (24 months *versus* 24.5 months).

Meanwhile, a similar meta-analysis of 21 studies between 1989 and 2008 was performed [Kang and Nam, 2009]. In this study, medium survival time was 27.5 months and optimal cytoreduction rate was 70%. Increasing median OS time (MST) was observed: with more recent year of publication, with increased percentage of taxane use, and increased rate of optimal cytoreduction. However, the number of NACT cycles before IDS and the proportion of patients with stage IV disease did not affect MST.

The latest retrospective studies verified the clinical significance of NACT-IDS. A Danish group compared the outcomes of NACT-IDS ($n = 515$) with PDS ($n = 990$). No difference in median OS was observed between PDS and NACT-IDS. However, patients without residual tumor had a better median OS when treated with PDS. In a multivariate analysis, NACT-IDS was associated with an increased risk of death after 2 years of follow up (HR 1.81, CI 1.39–2.35) [Fago-Olsen *et al.* 2014].

Based on these findings, NACT-IDS has become a primary treatment for patients with advanced EOC [Vergote *et al.* 2011b; Cornelis *et al.* 2012]. However, despite NACT being useful for patients in whom optimal debulking appears impossible, primary surgical cytoreduction should not be precluded by a lack of surgical skills and experience [Chi *et al.* 2012; Vergote *et al.* 2013].

Evaluation of effect of NACT

EOC staging is surgical and based on laparotomy findings with histological confirmation [Benedet *et al.* 2000]. Visual estimation by the surgeon is critical for the evaluation of intra-abdominal tumor spread. Whether the surgeons' statement of complete tumor resection is equal in primary surgery and in IDS remains unclear. NACT before surgery can cause fibrosis and adhesions in the peritoneal cavity and may interfere with the perioperative evaluation of tumor spread. Recently, a paper on the uncertainty of perioperative visual assessment of tumor dissemination after NACT was reported [Hynninen *et al.* 2013]. In this study, systematic visual evaluation of tumor spread was performed at the start of primary surgery/diagnostic laparotomy ($n = 39$) or interval surgery ($n = 16$). The peritoneal cavity was divided into 22 anatomical regions. The carefully documented results of the visual assessment were compared with the histopathological analysis of 220 biopsies from primary and 92 biopsies from interval surgery. In primary surgery, perioperative visual estimation of tumor spread showed 98% sensitivity, 76% specificity and 95% accuracy compared with histopathology. The difference in sensitivity and accuracy in primary and interval operations was statistically significant ($p < 0.001$). The authors concluded that in advanced EOC, microscopically carcinomatous areas have a benign visual appearance more often after NACT than at primary surgery. NACT may interfere with the perioperative visual evaluation of tumor spread and thus lead to incomplete resection of tumor in potentially resectable areas.

In the histopathological assessment, tumor response to NACT has been reported to cause observable microscopic changes such as tumor necrosis, fibrosis, macrophage infiltration and tumor-induced inflammation [Le *et al.* 2007; Wang and Zheng, 2013]. These variables have been shown to be significant prognostic factors in other solid tumors and may also be helpful in EOC treatment planning. Pathological assessment of 101 patients with EOC after NACT found that a high pathological tumor response score was the only significant predictor of time to disease-related death [Le *et al.* 2007]. Moreover, pathological features after NACT, such as fibrosis and necrosis, have been shown to affect outcomes in patients with EOC [Samrao *et al.* 2012]. Other researchers have shown the utility of histological assessment of surgical specimens after NACT [Muraji *et al.* 2013]. Outcomes were evaluated retrospectively in patients with advanced EOC or peritoneal cancer who received NACT consisting of paclitaxel and carboplatin followed by IDS. Therapeutic response was assessed histopathologically as grade 0–3, based on the degree of disappearance of cancer cells, displacement by necrotic and fibrotic tissue, and tumor-induced inflammation. Multivariate analysis showed that stage IV disease, residual cancer at the end of surgery of at least 1 cm, and histological grade 0–1 were independent predictors of decreased OS. Grade 0–1 was also an independent predictor of increased risk of relapse within 6 months.

As noted above, visual evaluation of NACT is difficult. Assessing the therapeutic effects of NACT

by histological specimens may be important in the choice of drug to be used in ACT.

Platinum resistance

Drug resistance after NACT and ACT has been found to correlate with *in vitro* drug resistance [Lim *et al.* 2010]. Several papers have shown the possibility of NACT inducing platinum resistance [Matsuo *et al.* 2010b; Chi *et al.* 2012]. The EORTC-NCIC randomized trial showed that surgery was less extensive in patients who received NACT, with associated reductions in mortality and postoperative complication rates. Nevertheless, NACT did not extend OS, perhaps due to tumor development of drug resistance.

The latest study comparing the response of chemotherapy in the PDS group and the NACT-IDS group was reported by Rauh-Hain and colleagues [Rauh-Hain *et al.* 2013]. The study population consisted of 425 patients, 95 (22.3%) underwent NACT-IDS and 330 (77.6%) underwent PDS. After the initial platinum-based chemotherapy, 42 (44.2%) women in the NACT-IDS group were considered to have platinum-resistant disease compared with 103 (31.2%) in the PDS group ($p = 0.01$). When multivariate logistic regression was used to control for factors independently associated with platinum resistance, NACT-IDS was no longer associated with an initial increased risk. However, in women who had a recurrence and were retreated with platinum-based chemotherapy, 32 (88.8%) in the NACT-IDS group had a recurrence within 6 months and were considered platinum resistant compared with 62 (55.3%) in the PDS ($p < 0.001$). The authors concluded that in women with EOC who have a recurrence and are treated again with platinum-based chemotherapy, NACT-IDS appears to increase the risk of platinum resistance. The data to support the clinical facts as described above are not clear. However, the possibility that ovarian cancer stem cells have remained in the abdominal cavity after NACT has been reported. After IDS, in which complete removal of macroscopic tumor tissue is achieved, residual cancer stem cells remain the in scar tissue. A population of chemotherapy-resistant stem cells selected during NACT and not debulked in IDS may play a role in EOC recurrence. It was suggested that all tissue showing traces of tumor, that is, scar tissue, should be removed during IDS [Lim *et al.* 2010]. More recently, another author reported that TP53-K351N mutation was involved in platinum resistance after NACT [Zhang *et al.* 2014]. However, at present, the possibility of NACT inducing chemotherapy resistance is unclear and further study is needed.

Recently, selection of chemotherapy regimens based on histology have attracted attention. The response rate of TC therapy for clear cell adenocarcinoma (CCC) and mucinous adenocarcinoma (MAC) is low compared with endometrioid adenocarcinoma and serous adenocarcinoma [Goff *et al.* 1996; Sugiyama *et al.* 2002; Shimada *et al.* 2009]. Efficacy of CPT-11 (CPT) against CCC has been confirmed *in vitro* and *in vivo* [Itamochi *et al.* 2002]. The Japanese Gynecologic Oncology Group (JGOG) carried out a prospective randomized phase II trial comparing CPT-cisplatin (P) therapy and TC therapy as initial chemotherapy for stage IC–VI CCC. Because, a favorable trend was observed for PFS in the CPT-P therapy group, an international randomized controlled phase III trial comparing CPT-P with TC is underway (GCIG/JGOG3017). It may be that CPT-P becomes an effective regimen of NACT for CCC. However, for MAC, the effectiveness of agents such as CPT, 5 fluorouracil and oxaliplatin used in gastrointestinal cancer has been studied [Sato *et al.* 2009]. Because an effective regimen has not been determined, NACT is not recommended for MAC. In addition, the effectiveness of NACT-IDS for nonepithelial ovarian tumors such as malignant germ cell tumor and yolk sac tumor has been reported [Lu *et al.* 2014; Talukdar *et al.* 2014].

The benefit of NACT relies on the correct selection of effective chemotherapy regimens. An assessment of the individual patient's chemosensitivity is essential for providing effective chemotherapy. In recent years, several biomarkers and methods for predicting the response to chemotherapy have been investigated [Kawaguchi *et al.* 2005; Naniwa *et al.* 2007; Matsuo *et al.* 2010a] but never used widely. Specific biomarkers need to be determined to identify patients most likely to benefit from NACT. Recently, new findings on clinical biomarkers useful in treatment selection (PDS or NACT-IDS) for advanced ovarian cancer have been reported. Exploratory *post hoc* analyses of registered cases in the EORTC55971 trial were performed. They found that the size of the largest metastatic tumor and clinical stage were significantly associated with the patient's prognosis. More specifically, patients with stage IIIC disease and metastatic tumors up to 45 mm benefited

more from primary surgery while those with stage IV disease and metastatic tumors larger than 45 mm benefited more from NACT [Van Meurs *et al.* 2013]. The authors concluded that both treatment options led to comparable survival rates for patients who did not meet these criteria. Further clarification of the treatment selection rule is necessary for progress towards individualized medicine.

Older patients

Older women with EOC are less likely to receive care from a gynecologic oncologist, undergo aggressive cytoreductive surgery and less likely to receive platinum-based chemotherapy or clinical trial participation [Hershman *et al.* 2004; Wright *et al.* 2008]. Oncologic outcomes among older women undergoing NACT-IDS appear similar to those undergoing PDS. The risk of readmission within 30 days of surgery was significantly greater among patients undergoing PDS compared with IDS. The increased risk of hospital readmission after PDS should be considered when contemplating NACT-IDS *versus* PDS as primary treatment [Worley *et al.* 2013]. Another study revealed that patients aged 70 years and over who underwent NACT had less perioperative morbidity after IDS, had improved complete cytoreduction to no residual disease (71.4% *versus* 28.1%), and there was no difference in OS or PFS [Glasgow *et al.* 2013]. A retrospective study evaluated use of NACT in patients aged 65 years and over. In their retrospective cohort, 20% of patients received NACT and there was no difference in rate of complications, rate of complete surgical resection or difference in OS and PFS [McLean *et al.* 2010].

A retrospective study from Memorial Sloan-Kettering found that 10% of their patient population received NACT because of advanced stage, medical comorbidities or advanced age (> 85 years). They found a statistically significant difference in OS (37 *versus* 50 months) and in PFS (13 *versus* 17 months) in patients treated with NACT *versus* PDS. They observed that in women who had complete surgical cytoreduction to no residual disease, the PFS was 24 months, which far exceeds the PFS of patients in the EORTC study (11 months). The authors concluded that primary debulking should continue to be the preferred management of patients with stage IIIC-IV EOC [Chi *et al.* 2012].

Wright and colleagues performed a population-based analysis to examine the effectiveness of upfront treatment strategies in 9587 older women (> 65 years old) with stage II–IV EOC. They found that use of PDS decreased from 63.2% in 1991 to 49.5% by 2007, whereas NACT increased from 19.7% in 1991 to 31.8% in 2007. Furthermore, in the observational cohort, survival with NACT did not differ significantly from that of PDS [Wright *et al.* 2014]. The importance of NACT-IDS in the initial treatment for older women with EOC will increase in the future.

Quality of life

NACT is thought to lead to improved QOL of patients. Patients with advanced disease frequently experience a variety of treatment- and disease-related side effects which may diminish their QOL. Patient-reported QOL has been recommended as an endpoint in clinical trials. The National Cancer Institute and the Food and Drug Administration mandated that the treatment goals should not only focus on survival but also on QOL. Numerous clinical trial protocols have included QOL as a secondary endpoint but until now only a few publications reported QOL outcomes in phase III ovarian cancer trials [Bezjak *et al.* 2004; Wenzel *et al.* 2005; Greimel *et al.* 2006; Rustin *et al.* 2011].

The EORTC trial included QOL as a secondary endpoint [Vergote *et al.* 2010]. Survival and QOL after NACT followed by surgery was similar to that after PDS followed by chemotherapy. However, institutions with good QOL compliance had a higher optimal debulking rate and better survival outcomes [Greimel *et al.* 2013]. Schwartz and colleagues reported that the NACT group had a poor PS and were significantly older compared with the PDS group in stage IIIC and IV cases; however, the length of hospital stay was significantly shorter in the IDS group [Schwartz *et al.* 1999].

These observations suggest that NACT plays an important role in maintaining QOL of patients with advanced EOC. Because advanced EOC is a disease that can rarely be cured, QOL should be evaluated as an endpoint in clinical trials of NACT.

Bevacizumab

Bevacizumab (Bev) is a humanized monoclonal antibody that recognizes circulating vascular endothelial growth factor. Several studies have

reported that Bev as first- or second-line treatment is active in patients with advanced EOC [Cannistra *et al.* 2007; Burger *et al.* 2011; Perren *et al.* 2011; Sato and Itamochi, 2012]. However, the use of Bev is not yet recommended in the neoadjuvant setting for the management of advanced EOC. This is because potentially problematic adverse effects unique to its mechanism of action could occur, which is especially important for surgical management. The most serious adverse events are gastrointestinal perforations, hemorrhages and arterial thrombolic events such as stroke and myocardial infarction. Gastrointestinal perforations associated with Bev used in the perioperative period have attracted attention because they seem to be more common in EOC than in other solid tumors [Han and Monk, 2007].

In the study by Cannistra and colleagues [Cannistra *et al.* 2007], patients were excluded if they had undergone major surgical procedure within 28 days. Despite the relatively good condition of the patients regarding adverse effects of Bev, the sponsor closed the study early because of a higher than expected incidence of gastrointestinal perforation (11.4%). In another study [Garcia *et al.* 2008], the exclusion criteria included serious, nonhealing wound ulcers and major surgical procedure. Among the 70 patients entered, three patients developed a gastrointestinal perforation, one a gastrointestinal fistula and another patient had a wound-healing complication. However, no cases of gastrointestinal perforations have been reported in other phase II trials evaluating Bev in the frontline setting [Burger *et al.* 2011]. Recently, Chereau and colleagues evaluated the safety and postoperative course of patients who had received Bev before debulking surgery for advanced EOC. They described the case of five patients who were initially judged to have inoperable disease and were revaluated after six courses of chemotherapy. The rate of postoperative complications was high (four among the five patients), but only one patient had a grade 3 or higher complication. None of the patients died in the postoperative course [Chereau *et al.* 2013]. Further investigation is necessary in order to confirm the usefulness of using Bev for NACT.

Conclusion

Noninferiority of NACT-IDS to PDS has been demonstrated in randomized controlled trials. However, there is still no evidence that NACT is superior to standard treatment. The biggest risk associated with use of NACT is that patients with significant side effects and refractory disease will lose the opportunity for initial surgery. Establishment of an optimal regimen is necessary in order to improve the outcome of NACT. Furthermore, the precise role of NACT in the management of advanced EOC has not yet been established. Importantly, well designed clinical trials of NACT are essential. Further studies to clarify the role of molecular targeted therapies in NACT are required.

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ORIGINAL RESEARCH

Contribution of transcription factor, SP1, to the promotion of HB-EGF expression in defense mechanism against the treatment of irinotecan in ovarian clear cell carcinoma

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Abstract

Ovarian clear cell carcinoma (OCCC) is a worst histological subtype than other ovarian malignant tumor. Heparin-binding epidermal growth factor-like growth factor (HB-EGF) is a promising target for ovarian cancer therapy. The aims of this study were to validate the efficacy of HB-EGF–targeted therapy for OCCC and to identify the transcription factor that contributed to the induction of HB-EGF by SN38 treatment in OCCC cells. HB-EGF was highly expressed in OCCC cells, and an increase of HB-EGF was induced by SN38 which had only antitumor effect among conventional anticancer agents on OCCC. A specific inhibitor of HB-EGF, a cross-reacting material 197 (CRM197), led to a synergistic increase in the number of apoptotic OCCC cells with the treatment of SN38. The luciferase assay with 5′-deletion promoter constructs identified a GC-rich element between −125 and −178 (the distal transcription start site was denoted +1) as a *cis*-regulatory region, and the treatment of SN38 induced luciferase activity in this region. An in silico and chromatin immunoprecipitation analysis estimated that SP1 bound to the *cis*-regulatory region of *HB-EGF* in OCCC cells. Real-time PCR and cell viability assays showed that the transfection of a small interfering RNA targeting SP1 suppressed the expression of HB-EGF induced by SN38, resulting in the enhanced sensitivity of SN38. Taken together, these results indicate that induction of HB-EGF expression contributed to defense mechanism against treatment of SN38 through the transcriptional activity of SP1 in OCCC cells.

Introduction

Ovarian cancer is the most lethal gynecological cancer in the Western world. Ovarian cancer usually has a poor prognosis because many cases are diagnosed in advanced stages. Standard treatment involves surgery, followed by chemotherapy including platinum derivatives (e.g., cisplatin [CDDP] or carboplatin) and taxanes (e.g., paclitaxel [PTX] or docetaxel). However, the 5-year survival rate of patients with advanced ovarian cancer has remained for the past three decades [1]. Ovarian clear cell carcinoma (OCCC), which is a common histological type in Japanese, is known to indicate significant drug resistance for conventional anticancer agents, resulting in a poorer prognosis. Moreover, the occurrence of OCCC, which links to endometriosis, has rapidly increased