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REVIEW

Neo-adjuvant chemotherapy for advanced stage endometrial carcinoma: a glimmer of hope in select patients

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Abstract
Purpose of review The objective of this review is to conduct a critical appraisal of the published literature on the use of neo-adjuvant chemotherapy followed by interval debulking in the treatment of stage IVb endometrial carcinoma patients.
Methods Narrative review of the pertinent literature on the application of neo-adjuvant chemotherapy and interval surgery in the treatment of advanced stage endometrial cancers.
Results Advanced stage endometrial carcinoma patients are treated by aggressive cytoreduction followed by adjuvant chemotherapy or by chemotherapy alone. The prognosis of patients that cannot undergo surgery is extremely poor. Preoperative reduction of tumor burden by chemotherapy can facilitate surgery in patients previously considered to have an unresectable disease, identify patients with chemo-sensitive tumors that are more likely to benefit from surgery, and enable a less aggressive surgery thus reducing morbidity. However, only 106 cases of neo-adjuvant chemotherapy were documented in the last two decades, majority (76) were described in retrospective case reports and case series. The available data may indicate feasibility of neo-adjuvant treatment in select patients. Compared to patients that had primary surgery, neo-adjuvant setting was associated with improved or equivalent survival and maximal debulking rates and reduced postoperative morbidity.
Conclusions Until further progress is reached, consideration can be given to recommending neo-adjuvant chemotherapy followed by interval debulking to patients with poor performance status or those patients who the surgeon believes would have suboptimal debulking if surgery was attempted.

Keywords Neo-adjuvant chemotherapy · Interval debulking · Advanced stage endometrial carcinoma

Introduction

Endometrial cancer (EC) is the fourth most common cancer in women and the seventh leading cause of cancer death in women of developed countries [1]. The majority of patients present with disease confined to the uterine corpus and have a favorable prognosis. Between 3 and 15 % of new EC cases will have tumor extending outside of the true pelvis or invasion of the bladder or rectal mucosa. Advanced cases account for more than 50 % of all uterine cancer-related deaths, with 5-year survival rates as low as 5–17.5 % [2]. Surgery is the mainstay of treatment. Early stage disease and low-risk tumors can be cured by surgery alone. Adjuvant treatments, radiotherapy and/or chemotherapy, are reserved for patients with adverse tumor features and advanced stage disease. Following the progressively increasing use of neo-adjuvant chemotherapy (NAC) in ovarian cancer patients, more physicians tend to employ neo-adjuvant chemotherapy followed by interval debulking and chemotherapy for advanced stage EC [3]. Establishing therapeutic algorithms for patients with tumors that have spread beyond the pelvis to involve intra-

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abdominal and extra-abdominal organs (stage IVb) is challenging due to the limited body of available evidence, small numbers of patients in most series, and the tendency to report on surgically and non-surgically treated patients in concert [4].

The purpose of this review is to critically appraise the application of neo-adjuvant chemotherapy in the treatment of advanced stage EC.

Materials and methods

Computerized literature search of electronic databases (PubMed, EMBASE, Cochrane Gynecological Cancer Review Group Trials Register and Cochrane Central Register of Controlled Trials) was performed for English language studies published between January 1990 and February 2015. Search terms used were endometrial cancer, endometrial carcinoma, uterine corpus cancer, stage IV, advanced stage, staging, debulking, cytoreduction, adjuvant, neo-adjuvant, and chemotherapy. Prospective and retrospective comparative observational studies and case–control studies comparing neo-adjuvant chemotherapy followed by interval debulking and adjuvant chemotherapy to primary surgery in the treatment of stage IV endometrial cancer as well as case reports of neo-adjuvant treatment in advanced EC were included.

Results

Advanced stage EC is a heterogeneous disease that may present as micro- or macroscopic peritoneal metastasis, pulmonary metastasis or intra-abdominal inoperable lesions. Most investigators consider patients with these different presentations in aggregate, despite their very different prognoses [5]. The current treatment paradigm for advanced EC has evolved over the past 3 decades to a multimodality approach that includes surgery, chemotherapy, and radiation therapy, with aggressive cytoreduction as the most crucial component. The NCCN Guidelines recommend palliative hysterectomy with or without chemotherapy, radiotherapy, or hormonal therapy for extra-abdominal disease [6]. The significance of aggressive maximal cytoreduction, to no visible disease, in patients with metastatic EC has been questioned. Generally, dismal prognosis associated with the disease, regardless of the treatment, relatively high, 36–39 %, intra/postoperative complications rate, advanced patients' age and associated comorbidities may all preclude optimal surgery [7]. However, multiple retrospective studies and meta-analyses demonstrated a statistically significant progression-free (PFS) and overall survival (OS) advantage when optimal cytoreduction was achieved [8, 9]. The addition of chemotherapy or chemo-radiotherapy to the treatment further improved survival rates [10, 11].

Some patients with stage IVb EC (17–59 %) cannot undergo surgery for their initial treatment either because of unresectable intra- or extra-abdominal metastases or due to their frail medical condition [12]. The prognosis of these patients is extremely poor, but detailed information regarding their treatments is lacking [4]. Current practice indicates either systemic (palliative) treatment or debilitating primary surgery. The neo-adjuvant setting, NAC, interval debulking surgery followed by chemotherapy, allows balancing between palliative chemotherapy (without surgery) and aggressive cytoreduction.

The data on the feasibility and practice of the neo-adjuvant treatment setting in advanced EC patients are limited to case reports and case series (Table 1). Resnik et al. were the first to describe NAC in EC patient [13]. In the following thirteen years, three additional case reports were published, describing initial response to NAC, the feasibility of maximal debulking and relatively extended survival [14–16]. In 2009, Vandenput et al. published their pivotal prospective study describing 30 stage IVb EC patients treated by NAC [7]. First, all patients underwent diagnostic laparoscopy to confirm the diagnosis and stage of disease, then received 3–4 cycles of platinum-based NAC followed by debulking surgery. 74 % of the patients had a complete or partial response to the neo-adjuvant chemotherapy. 14.3 % remained inoperable, but in 92 % of operated patients, maximal cytoreduction was achieved, higher compared to 18–75 % previously reported for primary cytoreduction [17]. Furthermore, median OS and PFS, as well as the postoperative complication rate were improved compared to previous reports on primary surgery [8]. Authors concluded that NAC resulted in a higher probability for complete surgical resection with less postoperative morbidity. Main criticism of this trial pertained to the fact that patients with lung and liver metastases were excluded from the study, which in theory, could have contributed to the higher rate of maximal cytoreduction [18]. Furthermore, a comparison arm of upfront debulking surgery would be needed to make any comment on the impact on PFS and OS.

Eto et al. presented a retrospective multi-institutional study of 426 Japanese stage IVb EC patients [4]. 279 patients had primary surgery followed by various adjuvant treatments. 59 patients received NAC followed by surgery and different postoperative treatments, chemotherapy only, radiotherapy alone, chemo-radiotherapy or no adjuvant treatment (Table 1). The initial complete or partial response to chemotherapy was 68 %. Compared to the primary surgery group, debulking to no visible lesions or lesions $\leq$1 cm was achieved in more patients, but did not

Table 1 Summary of publications on neo-adjuvant chemotherapy followed by interval debulking for advanced stage endometrial carcinoma (IVb)

Reference	Patients	Stage	Protocol	Response to NAC	Median DFS/ OS (months)[a]	Complications	Surgery results
Wilkinson [19]	10: 6 USC, 4 mixed	IVb	**NAC**: T/P 3-8 cycles **Postop**: T/P 2-12 cycles	90 % C/PR	10.4/17.3	10 % (minor)	70 % MD, 30 % ≤ 1cm Shorter surgery, Shorter hospital stay, Lower blood loss
Eto [4]	59: 24 non-endometrioid **Preop**: 57 chemo alone 2 chemo+RT **Postop**: 44 chemo alone 2 RT alone 5 Chemo+RT 8 no adjuvant trt.	IVb	**NAC**: 58 % T/P, 42 % D/P +/- other **Postop**: NA	68 % C/PR 15 % SD 12 % PD	NA/21	1.7 % (severe)	32 % MD 25 % </= 1cm 43 % > 1cm
Vandenput [7]	30: 27 USC, 3 mixed	IV	**NAC**: 3-4 cycles T/P 83 %, D/P 13 %, P 3 % **Postop**: T/P 2-5 cycles	CR 7 % PR 67 % SD 20 % PD 7 %	13/23	13 % minor 4 % severe	14.3 % inoperable 92 % MD[b] 8 % < 1cm[b]
Despierre [16]	2 USC	IVb	**NAC**: T/P x 3 cycles **Postop**: T/P x 5 cycles **NAC**: A/P x 3 cycles **Postop**: D/P x 3 cycles	SD PR	3 /24 29 /49		MD MD
Price [15]	3 USC	IIIc IVb IVb	**NAC**: T/P x 6 cycles **Postop**: T/P x 2 cycles **NAC**: T/P x 8 cycles **Postop**: Topotecan **NAC**: T/P x 6 cycles **Postop**: T/P x 2 cycles	CR PR CR	12 /20 12 /15 NA/17		MD MD MD
Le [14]	1 USC	IVb	**NAC**: T/P x 6 cycles **Postop**: RT	CR	NA/6		MD
Resnik [13]	1 USC	IVb	**NAC**:T/P x 3 cycles **Postop**: T/ P x 4 cycles	PR	7 /7		

NAC neo-adjuvant chemotherapy, *DFS* disease free survival, *OS* overall survival, *USC* uterine serous carcinoma, *RT* radiotherapy, *T/P* paclitaxel + carbo/cisplatin, *D/P* doxorubicin + carbo/cisplatin, *P* carbo/cisplatin alone, *NA* not available, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *MD* maximal debulking

[a] For case reports, DFS and survival are shown

[b] Percentage of patients that underwent interval debulking

reach statistical significance (57 vs. 45 %, $p = 0.087$, respectively). The median OS times of 21 months were almost similar between the groups ($p = 0.8351$). Severe postoperative complications were encountered in 1.7 % of NAC patients. Authors conclude that NAC may be a useful treatment option for highly selected patients with intra- or extra-abdominal stage IVb EC. Compared to the prospective study by Vandenput et al., in this study, 68 % (40) of patients had extra-abdominal disease including lung and/or liver metastasis. Although the largest study to report on NAC, this study may have a selection bias and several limitations. First, it is unknown which patients in the primary chemotherapy group were intended for the neo-adjuvant setting from the outset and which for palliative treatment only. Interpretation of the results is difficult because decision algorithms regarding initial treatment may vary among institutions. The quality of data may not be uniform because of the retrospective, multi-center design. Finally, a number of chemotherapy regimens were used before and after the surgery, the number of cycles given was not reported.

Wilkinson-Ryan et al. compared NAC to primary surgery in 10 and 34 EC patients, respectively [19]. In the NAC group, 90 % of the patients had partial or complete response to chemotherapy, all patients underwent debulking to no visible disease or lesions $\leq$1 cm and surgery was associated with a 10 % rate of minor complications. But, the median OS was 17.3 months, relatively short compared to previous reports. NAC patients had shorter operating times and hospital stays as well as lower blood loss. Women treated with NAC were more likely to have no gross residual disease and had fewer postoperative complications than those treated with primary surgery, but these differences were not statistically significant. Further, there was no difference in median PFS and OS between the 2 cohorts. However, this study is limited by a small sample size, single institution experience, and short follow-up time. With larger numbers and longer follow-up times, differences between the groups might have emerged.

Discussion

Clinical decision making for advanced stage EC should take into consideration patient's age, performance status (PS), morbidity attributed to primary debulking surgery, chemosensitivity, prognosis, and patient's quality of life. Administration of NAC identifies patients with a chemosensitive disease that are more likely to benefit from interval debulking surgery and adjuvant chemotherapy when compared to patients with chemo-resistant disease. Furthermore, resection of a reduced tumor burden permits less aggressive surgery, increases the rate of maximal cytoreduction, improving surgery associated morbidity and shortening operating times and hospital stays [7]. However, the paucity of data in literature to provide conclusive evidence to support this approach motivates many physicians to administer cytotoxic systemic treatment only.

Treatment strategies for advanced stage EC patients have evolved from hormonal therapy with progestational agents to radiation and chemotherapy [20–22]. The treatment approach that focuses on implementing aggressive surgical cytoreduction followed by adjuvant chemotherapy was modeled after the management of ovarian cancer (OC). Likewise, the application of NAC in EC patients with transperitoneal spread was extrapolated from the treatment of stage IIIc OC, considering that large comparative studies in advanced EC are unlikely to be feasible [7]. In advanced OC, NAC was first used as an alternative to primary debulking surgery in patients with apparently unresectable tumors or poor PS [23]. The indications for NAC were subsequently extended to include all cases of advanced disease, including patients with resectable tumors and good PS. However, the role of neo-adjuvant chemotherapy in advanced OC, a much more studied area than advanced EC, is still being debated [3].

EORTC-GCG/NCIC-CTG and the recently published CHORUS randomized trials showed that NAC followed by interval debulking surgery was not inferior to primary debulking surgery followed by chemotherapy as a treatment option for patients with bulky stage IIIc or IV OC [24]. The results of these studies remain controversial [25].

Particularly, the relatively low rates of debulking to residual disease $\leq$1 cm in the primary surgery cohorts were 42 and 41 %, respectively. However, the operating times in both trials were exactly the same for the primary and interval debulking groups, thus challenging the thoroughness of the surgical procedures [18]. One would expect that the NAC would have reduced the tumor burden to make the interval debulking surgery shorter. Conversely, perhaps more time spent during the primary debulking surgery might have achieved a higher rate of maximal dubulking.

Extrapolating treatments from advanced ovarian carcinomas to advanced EC may not be prudent. Although could be comparable at presentation, intra-abdominal lesions and peritoneal implants, stage IVb EC and stage IIIc OC have different biological characteristics and chemo-sensitivities [15]. Particularly, advanced EC does not behave as a chronic remitting disease state, as does OC, with the use of several consecutive lines of cytotoxic agents. Landrum et al. conducted a case-control study that compared intra-abdominal stage IVb EC with stage IIIc ovarian cancer [26]. They concluded that despite similarities in disease distribution and histology, overall survival for EC patients with intraperitoneal metastasis does not

approach that of patients with advanced OC. On the other hand, investigators in The Cancer Genome Atlas Research Network performed an integrated genomic, transcriptomic, and proteomic characterization of 373 endometrial carcinomas, and showed similar molecular features in uterine serous carcinomas and high-grade serous ovarian carcinomas, including similar focal somatic copy number alteration and gene-expression patterns. These subtypes share a high frequency of TP53 mutations and low frequency of PTEN mutations [27].

The majority of the described patients (60.3 %) had uterine serous cancer, a rare and aggressive histologic subtype of endometrial cancer, associated with a poor prognosis, high recurrence rate and poor response to adjuvant treatments [28]. Interestingly, 25 % of high-grade endometrioid cancers had serous-like molecular alterations associated with correspondingly aggressive clinical behavior, such as extensive copy number alterations, few DNA methylation changes, low estrogen receptor/progesterone receptor levels, and frequent TP53 mutations [29]. This finding may suggest comparable biologic aggressiveness and similar non-responsiveness to contemporary therapeutic algorithms, which can, in part, explain why histologic subtype was not an independent predictor of survival or response to chemotherapy in most publications [30].

Doxorubicin-based regimens were the mainstay of chemotherapy treatment for advanced EC for more than 2 decades [31]. GOG 209 is a phase III randomized trial which compared 1300 women with chemotherapy naive stage III, IV, or recurrent EC treated with carboplatin and paclitaxel or cisplatin, doxorubicin, and paclitaxel. The treatment outcomes of this trial revealed similar PFS and OS rate but a statistically significant reduction in the incidence of grade 2 or greater toxicity [32]. Carboplatin and paclitaxel combination is considered the standard treatment for advanced EC, with response rate of 50 % or higher in both neo-adjuvant and adjuvant settings. The NAC regimens used over the years (Table 1) reflect the trends in chemotherapy treatments for advanced stage ECs. New agents such as Bevacizumab are being investigated, and may be incorporated in future treatments [33].

The cornerstone of treatment of advanced EC is achieving maximal debulking in the safest manner while considering patients age and comorbidities. Unfortunately, there is no working algorithm or a single method to predict accurately the probability of maximal debulking in either ovarian cancer, let alone, in the less investigated advanced EC [34]. In most publications, NAC was presented to patients at the discretion of the treating physician. Vanderput et al. were unique in assessing extent of disease with laparoscopy before offering NAC.

Preoperative evaluation with CT or fusion PET/CT scans may identify patients with extensive disease. However, algorithms predicting maximal debulking, such as proposed by Suidan et al. for ovarian cancer, are yet to be validated more broadly [35]. Laparoscopy has been used to triage for resectability. But, a recent Cochrane review indicated that using a laparoscopy-based prediction models for OC does not increase the sensitivity, and will result in more unsuccessful debulking operations [36].

In conclusion, advanced stage EC patients are treated by aggressive cytoreduction followed by adjuvant chemotherapy or by chemotherapy alone. Application of NAC can assist in identifying patients with chemo-sensitive disease that are more likely to benefit from a debulking surgery. It is presumed that preoperative reduction of tumor burden by chemotherapy can facilitate a less aggressive surgery thus reducing operative morbidity, shortening operating time and hospitalization, and improving patients' quality of life. The available data indicate that NAC was well tolerated in patients with unfavorable disease-related characteristics, maximal debulking rates were higher, complications rate lower and hospital stay shorter compared to patients that had primary surgery. However, only 106 cases of NAC were documented in the last two decades, majority (76) were described in retrospective case reports and case series, subject to inherent limitations and biases. Therefore, no general recommendations can be drawn from the existing data. Prospective trials can definitively determine the role of NAC in advanced EC and identify preoperative characteristics of patients that will benefit most from NAC. Until further progress is reached, consideration can be given to recommending NAC followed by interval debulking in a trail setting to patients with poor performance status or those patients who the surgeon believes would have suboptimal debulking if surgery was attempted.

Compliance with ethical standards

Conflict of interest Author declares no conflict of interest.

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