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Taxanes: Their Impact on Gynecologic Malignancy

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Abstract

The use of taxanes in the treatment of gynecologic malignancies expanded tremendously over the past 30 years. Both paclitaxel and docetaxel have unique microtubule stabilizing, antiangiogenic and radiation sensitizing properties that endow them with remarkable activity as chemotherapeutic agents. As research into the appropriate dose, timing, treatment interval and response rates have been studied, they emerged as one of the most active agents available in the treatment of gynecologic cancer. The body of research on taxanes continues to expand especially in regard to the use of taxanes in alternative formulations and in combination with newer treatments or routes of treatment. This review focuses on the development of taxanes as an effective therapy in the treatment of gynecologic cancers and data currently available in the literature regarding their efficacy. Future directions of taxane based chemotherapy in regards to ovarian, uterine and cervical cancers are also addressed. There is little doubt that taxane based chemotherapy will remain an integral part of the treatment of gynecologic cancer for the foreseeable future.

Keywords

Taxane; paclitaxel; docetaxel; cervical cancer; ovarian cancer; endometrial cancer

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Paclitaxel (Taxol®), originally isolated and formally characterized in 1971 from extracts from the bark of the pacific yew tree, and its semisynthetic analog docetaxel are microtubule-stabilizing agents endowed with remarkable cytotoxic activity against a variety of human tumors. Over the past 30 years taxanes have been implemented in the treatment of gynecologic malignancies and found to play an important role in the management of cancers of the ovary, uterus and cervix.

Taxanes in the treatment of ovarian cancer

Introduction

Ovarian cancer is the most deadly of all gynecologic cancers. According to the National Cancer Institute, approximately 22,240 new cases will be diagnosed and 14,030 deaths will occur in 2013. The most common form of ovarian cancer is epithelial ovarian cancer (90%) with serous, endometrioid, mucinous, and clear cell being the 4 most common types. Recent

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evidence has suggested that some epithelial tumors, especially high grade serous tumors, may arise from the distal end of the fallopian tube [1]. Upon diagnosis, patients are either given neoadjuvant chemotherapy or undergo debulking surgery with hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic and paraortic lymphnode dissection, pelvic washings and multiple random peritoneal biopsies. Ultimately, the goal of surgery is optimal cyto-reduction where at the completion of surgery all remaining disease is less than 1 cm in size. Ovarian, fallopian tube, and primary peritoneal cancer are all treated using similar approaches both surgically and in chemotherapeutic regimens. Despite the development of new chemotherapeutic regimes, carboplatin with paclitaxel remains the first line treatment for ovarian cancer.

Paclitaxel's use in ovarian, fallopian tube and primary peritoneal cancers

Early phase I trials testing paclitaxel at doses ranging from 15–230 mg/m² found promise in the treatment of a variety of solid tumors including platinum resistant ovarian cancer [2]. Toxicity of paclitaxel included mucositis, alopecia, leukopenia, thrombocytopenia and neuropathy. The first phase II studies looked at paclitaxel's effect on advanced and chemotherapy resistant ovarian cancers. Published in the *Annals of Internal Medicine* in 1989, McGuire found that of 47 patients with ovarian cancer treated with paclitaxel alone 12 were noted to have partial or complete response. Decreased residual tumor was noted through the use of imaging studies, corresponding to a response rate of 30%. It was also noted that responses to therapy were seen with as few as one and up to six doses of paclitaxel. This study used on average 50% lower dosages (110–170 mg/m²) compared to the phase I studies with durability of response from 3–15 months. [3] Similar response and duration of response were seen in other phase II trials. [4, 5]

Paclitaxel showed promise in treating multidrug resistant ovarian cancer. However, it's toxicity and hypersensitivity reactions would limit its use clinically if the toxicity could not be mitigated. Previous studies had shown that hypersensitivity reactions commonly occurred with paclitaxel use especially if given as a bolus and at higher doses [6]. The nature of the reactions and early onset during infusion made investigators believe they were hypersensitivity reactions similar to those seen with intravenous contrast. These reactions were successfully treated with corticosteroids, antihistamines and prolonging infusion times [2–7]. Development of pretreatment regimens helped to reduce the frequency of hypersensitivity reactions related to the Cremophor in the paclitaxel preparation. In earlier trials, paclitaxel's toxicity precluded its use as outpatient treatment. Pretreatment was shown to drastically reduce hypersensitivity reactions giving hope that paclitaxel could be used as an outpatient therapy [8,9]. Eventually studies showed that even if hypersensitivity reactions did occur future treatments could still be administered if desensitization protocols were followed [10].

Many trials thereafter focused on decreasing infusion times from 24 to 6 to 3 and eventually to 1 hour. Ultimately the goal was to be able to offer a safe, effective and reasonably efficient outpatient treatment for ovarian cancer patients. The results from the European-Canadian high versus low dose paclitaxel and short versus long infusion trial were published. The goal of the study was to determine the dose-response relationship of

paclitaxel and the safety profile of paclitaxel given as a short infusion with premedication. They successfully demonstrated that the use of 175 mg/m² of paclitaxel had a slightly better response rate in terms of progression free survival(PFS) compared to 135 mg/m², however, the duration (3 vs. 24 hrs) of the infusion had no effect on PFS. Results also suggested that infusion over 3 hours with premedication was safe, hypersensitivity reactions were rare, and less neutropenia was observed. [11] As a result of this study dosages of 175 mg/m² were commonly used. In 1995, Hainsworth successfully demonstrated infusion with paclitaxel was possible over a one hour time frame if patients underwent pretreatment with dexamethasone, diphenhydramine, and cimetidine. Again the shorter infusion times were associated with less bone marrow toxicity but same efficacy as prolonged infusions [12]. Prior to studies relating myelosuppression with length of paclitaxel infusion, neutropenia was the dose-limiting toxicity in most trials [13–18]. Phase I and Phase II studies looked at the use of granulocyte colony stimulating factor (G-CSF) after paclitaxel administration and its ability to prevent leukocytopenia and thus prevent change in dosing regimens [15,19–21]. They found that using G-CSF in conjunction with paclitaxel could prevent neutropenia in most patients while still achieving tumor response rates in the 30–40% range; however, it now appeared that shortening the infusion time would decrease the rate of neutropenia and decrease the need for G-CSF. With most of the toxicity of paclitaxel and therapeutic interventions elucidated there was a push to more phase II and III studies.

In September of 1994 the Gynecologic Oncology Group (GOG) published a phase II trial assessing the use of paclitaxel in both platinum sensitive and platinum resistant ovarian cancer patients [22]. During this trial, patients with biologically aggressive ovarian cancers were treated with 170 mg/m² of paclitaxel over 24 hours every three weeks while undergoing treatment with or without concomitant platinum-based chemotherapy. The platinum resistant arm of the study had a response rate of 33% while the platinum sensitive arm had a response rate of 44%. [22] Significant improvement in response rates were observed when paclitaxel and platinum were given together. As a result trials were developed to investigate their use in conjunction.

Early pharmacokinetic studies showed that paclitaxel and platinum compounds could be safely given together with little pharmacodynamic interaction [23]. Prior to development of paclitaxel, cisplatin was typically given with cyclophosphamide. The GOG demonstrated in study 111 that use of paclitaxel at 135 mg given over 24 hours followed by cisplatin 75 mg/m² was superior to cisplatin and cyclophosphamide (750 mg/m²) when each was given every 3 weeks with response rates of 73% compared to 60% respectively. The complete response rate in this study was 51% compared to 36% in the paclitaxel and cyclophosphamide arms respectively. The GOG also showed significant improvement in progression-free survival from 13 to 18 months and overall survival from 24 to 38 months with the use of cisplatin and paclitaxel together. [24] Equivalent improved response rates were seen in subsequent phase one trials with the less toxic platinum drug, carboplatin, in combination with paclitaxel [25]. Paclitaxel's superiority to cyclophosphamide in combination with platinum-based chemotherapy was later confirmed in 2000 by Piccart et al. in a phase III randomized controlled trial. Piccart successfully demonstrated in the European Canadian intergroup trial (OV10) that paclitaxel compared to cyclophosphamide improved overall (59% vs. 45%) and complete response rates (41% vs. 27%), better

progression free survival (15.5 months vs. 11.5 months), and improved overall survival (35.6 months vs. 25.8 months) [26]. All data to this point suggested that paclitaxel with platinum-based chemotherapy should be used as first line treatment in ovarian cancer.

The effectiveness of paclitaxel as a first line chemotherapeutic drug for ovarian cancer came into question after the results of GOG 132 were published in 2000. The results of GOG 132 suggested no superiority between the three treatment arms which were single-agent paclitaxel, single-agent cisplatin, and concomitant use of both drugs [27]. These data contradicted previously published phase III studies. Upon further analysis the contradictory results were thought to be related to the significant cross over between the different treatment arms prior to progression of disease. International Collaboration Ovarian Neoplasm 3 trial (ICON3) evaluated paclitaxel's effect in combination with carboplatin in comparison to two control arms carboplatin alone vs. cisplatin, doxorubicin, and cyclophosphamide. It also found no differences in response rates, progression free survival, or overall survival with single-agent carboplatin, carboplatin with paclitaxel, or cisplatin, doxorubicin, cyclophosphamide [28]. Compared to cisplatin in GOG132, carboplatin did not have enhanced toxicity and could have been selected as the standard regimen for subsequent studies. However, results of GOG 111 and OV10 were encouraging enough to widen the adoption of paclitaxel with a platinum as the preferred first line treatment for ovarian cancer. [24, 26]

In 2003 ICON 4/Arbeitsgemeinschaft Gynäkologische Onkologic –Ovary 2.2 trial (AGO-OVAR-2.2) examined the use of platinum chemotherapy with and without concomitant paclitaxel in recurrent ovarian cancer. The use of platinum and paclitaxel together significantly improved progression free survival by 10% or median of 3 months. [29] These results confirmed the importance of paclitaxel use in recurrent ovarian cancer.

The combination of carboplatin and paclitaxel continues to be the mainstay of treatment of epithelial ovarian cancer throughout the world. It is the standard to which all other chemotherapeutic drugs are compared. While the use of paclitaxel as consolidation treatment after first-line paclitaxel/platinum-based regimens has not been shown to prolong progression-free survival or overall survival in patients with a complete response [30], in the last few years data supporting the use of paclitaxel in weekly (dose dense) schedule as opposed to dosing every three weeks have emerged. Paclitaxel administered on a weekly basis in the primary setting improved progression free survival from 17.2 to 28.0 months and overall survival from 62.2 months to 100.5 months at the cost of slightly higher toxicity in the form of grade 3 and 4 anemia [31]. Weekly dose dense regimens have also been suggested to be efficacious in those with platinum and paclitaxel resistant ovarian cancer. Response rates to dose dense weekly paclitaxel of 20.9% were seen in patients with ovarian or primary peritoneal cancer resistant to both platinum and paclitaxel while response rates were as high as 60% in those with platinum resistant ovarian cancer [32, 33]. Data from first-line trials comparing carboplatin and paclitaxel to the combination of carboplatin with either gemcitabine or pegylated doxorubicin suggest that carboplatin with paclitaxel is equivalent or superior therapy [34, 35]. Trials have also looked at the addition of topotecan or gemcitabine to the standard carboplatin paclitaxel regimen which did not improve survival in ovarian cancer. [36–38]

Despite the development of multiple well-tolerated chemotherapies, carboplatin and paclitaxel are still considered first line treatment for ovarian, fallopian tube, and primary peritoneal cancer. Evidence suggests that the use of each drug improves overall survival and that the discovery of paclitaxel and its characterization in 1971 revolutionized the way that these cancers were treated. The development of other chemotherapy in addition to paclitaxel has continued to provide improved long term survival to patients and encouraged translational research in the hope of discovering a potential cure for recurrent ovarian cancer. Current studies are focusing on using paclitaxel through the intra peritoneal route as well as its use in conjunction with nanoparticles [39,40]. Studies are also ongoing into the development of nanocrystalline paclitaxel for potential use in hyperthermic intraperitoneal chemotherapy [41]. In 2006 the GOG published the results from study 172 which showed an increase in overall (49.7 to 65.8 months) and progression free survival (18.3 to 23.8 months) with the use of IV paclitaxel followed by IP cisplatin and IP paclitaxel compared to standard therapy with IV paclitaxel and IV cisplatin [42]. Critics of this study have argued that the two arms of the study received different total dosages of drug and that the standard treatment arm of the study should have received carboplatin rather than cisplatin. Toxicities associated with the IP route including pain and other catheter related problems were also noted to be relatively high at 34% [42]. However, studies have shown improved overall survival (from 47 to 84 months) in patients treated with paclitaxel IV followed by cisplatin and paclitaxel IP compared to IV cisplatin and paclitaxel in patients with BRCA 1 mutations and ovarian cancer [43]. Data from recent studies have made this route of infusion one of continued interest. Recent phase II studies in platinum sensitive recurrent ovarian, fallopian tube and primary peritoneal cancer have shown strong response rates (64%) with single-agent nanoparticle albumin bound paclitaxel [44]. The properties of paclitaxel and its ability to stabilize microtubules, inhibit conversion to spindle apparatus, and antiangiogenic properties have made paclitaxel an integral part of the treatment of ovarian cancer as an every 3 week regimen using 180 mg/m² given over 3 hours or as a dose dense regimen at 80 mg/m² on days 1, 8, and 15 every 3 weeks [31].

As a result of data from GOG 172 and improved response rates with dose dense paclitaxel elucidated in JGOG 3016 at least three ongoing phase III studies have been designed to assess the activity of IP carboplatin and dose dense paclitaxel (i.e., GOG 252, Japanese GOG 3019 trial, and the Canadian National Cancer Institute led OV-21/GCIG study). The results of these studies are highly anticipated and should help clarify the role of IP chemotherapy in the setting of dose-dense paclitaxel. Results of recent studies suggest that paclitaxel will continue to be a critical part of treatment for years to come.

Docetaxel's use in ovarian, fallopian tube and primary peritoneal cancers

Early research with paclitaxel was slowed by the relative difficulty in obtaining the bark of pacific yew tree and the extract needed for conducting on going trials. After paclitaxel's discovery, the pacific yew tree was being harvested at an alarming rate making the need for the development of synthetic taxane a priority. From this need arose the challenge of creating the drug from a renewable resource. Researchers in Rhone Poulenc Rorer in collaboration with the French Centre National de Recherche Scientifique were the first to synthesize a semisynthetic form of paclitaxel from the needles of the European yew tree

which they named docetaxel [45]. Docetaxel like paclitaxel showed early signs of antimitotic activity in in-vitro and mouse studies. Some data even suggested that it might be superior to paclitaxel in its activity noting nearly 3 fold greater log kill than paclitaxel [46]. This new semisynthetic drug from a renewable resource was quickly pushed into phase one trials.

Phase one studies showed that the new compound like paclitaxel was successful in treating patients with ovarian cancer and could be safely administered at 100 mg/m² over one hour every 21 days [47]. Dose limiting factors were granulocytopenia and mucositis which were reported in many patients receiving docetaxel [47–49]. There were also reports of neutropenic fever in up to 48% of patients and rarely sepsis that were caused by the combination of neutropenia in the presence of mucositis [48, 50]. Compared to paclitaxel cardiac arrhythmias and hypersensitivity reactions were not seen as frequently and neuropathy was less severe. Some side effects were noted that had not previously been seen with paclitaxel including higher rates of neutropenia, fluid retention and desquamation over the extremities. Some have suggested that the differences in the toxicity profiles of these two similar drugs could be attributed to the way that docetaxel is retained for longer periods of time within cells [51].

Phase II clinical trials with chemotherapy-refractory ovarian cancer patients showed similar response rates to those seen in earlier trials with paclitaxel with approximately 30% responding to docetaxel therapy and durability of response ranging from 4–17 months [50, 52] Reports also suggested that docetaxel could potentially be considered a salvage therapy for patients with paclitaxel resistant ovarian cancer with response rates of 22–23% [53, 54]. In 2001, Markman showed that docetaxel combined with carboplatin was an efficacious treatment for ovarian, fallopian tube and primary peritoneal cancer with a response noted in 32 of 42 patients using lower doses than previously reported [55]. These promising results led to a large randomized controlled trial, the Scottish Randomized Trial in Ovarian Cancer (SCOTROC), which compared response rates and toxicity of docetaxel with those of paclitaxel.

The results of the SCOTROC phase III clinical trial comparing the use of paclitaxel to docetaxel combined with carboplatin in over 1000 patients were published in 2004. Relatively identical efficacy was seen with overall survival rates of 64 and 68%, tumor response rates of 58 and 59% with docetaxel and paclitaxel respectively. The largest difference between the two treatments was their toxicity. Grade 3 and 4 neutropenia were noted more frequently with Docetaxel while neuropathy was more common with paclitaxel. At the end of the study it was concluded that docetaxel (60–75 mg/m²) is an effective alternative to paclitaxel for first line treatment of ovarian cancer and today is considered an alternative first line treatment in epithelial ovarian cancer, especially for patients at higher risk of neuropathy [56, 57].

Conclusion

Taxanes have played a key role in the treatment of ovarian, fallopian tube, and primary peritoneal cancers. With the discovery and development of paclitaxel, docetaxel, and nab-

paclitaxel survival has improved. Despite the discovery of taxanes over 40 years ago, they continue to be a key component in the treatment of epithelial ovarian cancer.

Taxanes in the treatment of Endometrial Cancer

Introduction

Endometrial cancer is the most common gynecologic cancer in the Western world. The most common histologic type is endometrioid adenocarcinoma. This subtype accounts for approximately 80% of cases. Most endometrial cancers are diagnosed at an early stage after presentation to their gynecologist with post-menopausal or abnormal vaginal bleeding. Typically endometrial cancers are classified as type 1 or type 2 cancers. Type 1 endometrial cancers are endometrioid in histology and associated with increased levels of estrogen and progesterone receptors as well as higher serum estrogen levels. Type 2 endometrial cancers are most commonly clear cell or serous in histology and are not associated with hyperestrogenic state. The initial management of endometrial cancer includes surgical staging followed by adjuvant chemotherapy or hormonal therapy with or without radiation therapy.

Initial treatment of endometrial adenocarcinoma

Type 1 endometrial cancers are endometrioid adenocarcinomas in histology. They are considered to have a better prognosis and are associated with hyper estrogenism [58]. This histotype is often managed with surgery followed by vaginal cuff brachytherapy or pelvic radiation therapy depending on stage and histology. Patients diagnosed with either advanced or recurrent disease are typically treated with chemotherapy and/or hormonal therapy. In advanced endometrial cancer, a randomized controlled trial showed a significant benefit of chemotherapy when compared to whole abdominal radiation. Pelvic radiation also has been the traditional adjuvant treatment for endometrial cancer patients but four large trials failed to show an improvement in overall survival compared to observation alone following surgery [59–62]. These trials suggested that patients may have micro-metastatic disease spread outside the irradiated field and could potentially benefit from systemic chemotherapy with or without pelvic radiation therapy.

Single cytotoxic agents have been reported to have response rates as high as 40% in chemo-naïve metastatic endometrial cancer patients [63]. The anthracyclines, platinum compounds and taxanes are the most common agents used alone or in combination [64, 65]. Doxorubicin monotherapy and cisplatin/doxorubicin (AP) combination therapy have been compared by Gynecologic Oncology Group (GOG) 107 study and European Organization for Research and Treatment of Cancer (EORTC) 55872 study. Both studies showed superior response rates with the doxorubicin and cisplatin combination compared to doxorubicin alone [66, 67]. Although adding cisplatin to anthracycline containing chemotherapy regimens improved response rates and progression-free survival, more trials were underway evaluating the use of paclitaxel in the management of patients with advanced or recurrent endometrial cancer [68]. Objective response rates of up to 73% have been reported with paclitaxel and platinum-based triplets [69]. Data from phase II trials have demonstrated the biological and clinical activity of paclitaxel with objective response rates around 30% in

patients with aggressive and previously treated endometrial cancer. [70–72]. These trials provided support to the evolving idea that taxanes were the most active chemotherapy in endometrial cancer.

The activity of the taxanes elucidated in early trials lead to initial phase III trials using taxanes in combination with other chemotherapeutic regimens including epirubicin with platinum (TEP) and doxorubicin with platinum (TAP). Lissoni et al reported on the TEP regimen (paclitaxel, epirubicin, and cisplatin). This regimen showed significant anti-tumor activity in advanced endometrial carcinoma [69, 73]. This eventually lead to the use of paclitaxel, epirubicin and carboplatin which have shown improved activity against metastatic and recurrent endometrial carcinomas. Bone marrow toxicity noted with this regimen was relatively tolerable with G-CSF support [12]. In 2004 findings from GOG 177 were published. This study compared paclitaxel in the treatment of recurrent or metastatic endometrial cancer in combination of doxorubicin and cisplatin (TAP) with the standard therapy of doxorubicin and cisplatin (AP). This trial was the first randomized study to show a statistically significant improvement in overall survival in recurrent or metastatic endometrial cancer [74]. Compared to AP, TAP improved response rates from 34% to 57%, progression-free survival from 5.3 to 8.3 months and overall survival from 12.3 to 15.3 months [74]. During this study the TAP regimen was found to have increased toxicity compared to the doxorubicin and cisplatin regimen, with 39% compared to 5% grade 2–3 peripheral neurotoxicity in each arm respectively. This was followed by a phase III trial comparing TAP with carboplatin and paclitaxel. This non-inferiority trial confirmed that the carboplatin plus paclitaxel regimen compared to TAP provided similar median progression-free survival (14 months versus 14 months hazard ratio 1.03) and median overall survival (32 months versus 38 months hazard ratio of 1.01) respectively. As a result the TAP regimen has mostly been replaced by the equally effective and less toxic carboplatin and paclitaxel regimen in the treatment of advanced and recurrent endometrial carcinoma [75,76].

Endometrial cancer has long been treated with radiation therapy. Trials now sought to find if the radio-sensitizing properties of paclitaxel could improve responses to radiation therapy and improve overall tumor kill. Carboplatin and paclitaxel were investigated alone and in conjunction with radiation therapy in a phase II study of advanced and recurrent endometrial cancer with response rates were between 45–78% [68]. The current GOG experience with radiotherapy followed by chemotherapy was reported by Homesley et al and showed reasonable efficacy despite the fact that 20% of patients were not able to complete all prescribed therapy due to hematologic toxicity [77]. As a result, the sandwich method of delivering these two modalities has been suggested because this regimen has the potential to be as efficacious with less systemic toxicity. Studies have assessed the feasibility and efficacy of administering docetaxel and carboplatin chemotherapy followed by pelvic radiotherapy and finally consolidation chemotherapy for patients with advanced or recurrent endometrial cancer. This approach was found to be feasible, active and well-tolerated with a 3 year progression-free survival of 71% and overall survival of 90% in patients with advanced stage endometrial cancer [78].

The GOG is seeking to determine the appropriate use of radiation with carboplatin and paclitaxel in GOG-249. This trial is a phase III study of pelvic radiation therapy versus

vaginal cuff brachytherapy followed by paclitaxel (175 mg m²) and carboplatin (AUC of 6) chemotherapy for 3 cycles in patients with high-risk early-stage endometrial cancer. Currently two randomized phase III trials, GOG-258 and post-operative radiotherapy in endometrial cancer 3 (PORTEC3), are investigating the use of platinum and taxane-based chemotherapy with and without radiation therapy in patients with advanced endometrial cancer. Data from these trials will help to define the role of chemotherapy and radiation therapy in advanced endometrial cancer.

Taxanes have an important role in the management of type II endometrial cancers. These endometrial carcinomas are non-estrogen related and include grade 3 endometrioid, serous, and clear-cell histotypes [79]. Type II endometrial cancers account for a minority of cases and are associated with unfavorable prognosis due to their aggressive biologic behavior and higher rate of recurrence [58]. Uterine serous carcinoma (USC) represents the most aggressive variant of Type II endometrial cancer [80]. Although this tumor subtype constitutes less than 10% of all endometrial tumors, it accounts for 39% of deaths due to endometrial cancer [81]. At the time of surgical staging 37–70% of patients with USC demonstrate extrauterine disease [82, 83]. First-line therapy for USC traditional begins with surgical staging followed by platinum/taxane combination chemotherapy for advanced disease [84, 85]. A recent study demonstrated that adjuvant carboplatin/paclitaxel chemotherapy and concurrent intravaginal radiation are not only well tolerated but also provide excellent outcomes in patients with early stage USC. 5 year disease-free survival and overall survival rates were 85% and 90% respectively [86]. The current NCCN guidelines for patients with early stage USC with myometrial invasion recommend surgical staging followed by adjuvant chemotherapy with or without tumor-directed radiation [87]. Surgery alone for USC even if early stage has not been shown to be as effective as multimodal therapy with recurrence rates of up to 30% in stage I disease and 50% in stage II disease with surgical management only [88, 89].

Treatment of uterine sarcoma

The taxanes have also been utilized with acceptable response rates in uterine leiomyosarcomas. Gemcitabine and docetaxel had better efficacy compared to gemcitabine alone in a phase II trial of patients with metastatic soft tissue sarcomas [90]. Since carcinosarcomas are rare, patients are included in clinical studies of other types of uterine sarcomas. Recurrences develop in up to 50% of patients with early stage disease; therefore adjuvant chemotherapy and radiation therapy are often given. The combination of carboplatin, paclitaxel and pegylated liposomal doxorubicin was found to be active in advanced, persistent or recurrent endometrial carcinosarcoma with an acceptable toxicity profile [91].

Treatment of recurrent endometrial adenocarcinoma

Factors governing potential benefit from chemotherapy in patients with advanced or recurrent endometrial cancer have not been well elucidated. Adverse prognostic factors noted in previous studies included higher grade, older age, prior irradiation, liver metastases, other intra-abdominal disease, short time to first recurrence, and African-American race [74, 92, 93]. A previous study evaluated the prognostic factors in 110 patients treated with

paclitaxel-based combination therapy. Data suggested that performance status at diagnosis and relapse within a previously irradiated field independently predicted survival [94]. Multiple studies have shown that a good performance status at the time of diagnosis of recurrence has been consistently associated with improved survival [67, 74].

When endometrial cancer recurs after first-line chemotherapy it is largely a chemo-resistant disease. There are few randomized trials to guide treatment in this setting. The majority of the evidence used to help treat these patients is gathered from subgroups treated as a part of phase II studies [64]. Paclitaxel has consistently shown the best antitumor activity in this patient population with response rates of greater than 20% [71, 72]. Data have also suggested that treating patients with paclitaxel at the time of relapse, even after initial treatment with carboplatin and paclitaxel, can achieve a fairly significant objective response rate [95]. Further support for the taxanes as efficacious chemotherapy in recurrent disease was shown using docetaxel in combination with topotecan. This combination showed clinical benefit and was well-tolerated in heavily pretreated patients with recurrent uterine cancers [96]. While taxanes have had success in treating primary and recurrent uterine cancers, some tumors develop resistance after taxane exposure. Mechanisms for taxane resistance have been investigated and data from several research groups have found a strong correlation between the level of tubulin- β -III expression and taxane resistance, suggesting tubulin- β -III upregulation is important for taxane resistance in tumors [97].

Conclusion and future directions

Continued study of alterations in cell cycle regulation, chemotherapeutic response, and development of resistance has led to the use of combination molecular targeted therapy with cytotoxic chemotherapy. In normal cells, the PIK3/AKT/mTOR pathway is tightly controlled, but a large number of cancers harbor genetic mutations that result in the dysregulation and activation of this pathway. This enables tumors to metastasize and invade normal tissues. These alterations allow them to grow despite conditions where nutrients and oxygen are scarce. Furthermore, these changes can make them resistant to radiation and chemotherapy [98–100]. Targeting the PIK3/AKT/mTOR pathway using potent and selective dual PIK3CA/mTOR inhibitors may therefore represent a compelling therapeutic strategy against biologically aggressive endometrial cancer. The use of PI3K/mTOR inhibitors along with cytotoxic chemotherapy, including taxanes, may not only potentially counteract tumor resistance but also may be potentially synergistic and thus prove to be an efficacious strategy for treatment of these tumors [101].

Taxanes in the treatment of cervical cancer

Introduction

Cervical cancer represents 13% of cancers of the female genital tract, with an estimated 12,340 new cases and 4,030 deaths projected for the United States in 2013 [102]. Human papillomavirus is implicated in > 99% of cervical cancers [103]. Squamous cell histology constitutes 69% of cases; adenocarcinomas represent the second most common histology (25%). Mucinous, clear cell, serous, adenosquamous, and glassy cell adenocarcinomas, as

well as neuroendocrine tumors constitute the minority of cases. Independent of histotype, clinical staging determines potential treatment modalities that may be implemented.

Initial Management

Early stage cervical cancers including IA1, IA2, and non-bulky carefully selected IB1, IB2, and IIA can undergo primary surgical treatment. Patients with high-risk (e.g., nodal metastases or positive margins) or intermediate-risk (i.e., 2: lymphovascular space invasion, stromal invasion > 1/3, tumor > 4 cm [104]) are candidates for adjuvant treatment using post-operative external beam radiotherapy with or without non-taxane based chemotherapy [105, 106]. Traditionally, bulky IB1 and IB2 disease has been treated with extrafascial hysterectomy following chemoradiation. Stage IIB and greater disease generally warrants external beam chemoradiation with concomitant cisplatin therapy followed by intracavitary radiation therapy. In 1999, the National Cancer Institute released a statement that recommended chemoradiation as a standard approach to locally advanced cervical cancer, prompted by the results of GOG-85, RTOG-9001, GOG-120, and GOG-123, among other studies [107–110].

This conventional management has been challenged. Some studies have suggested the use of neoadjuvant chemotherapy followed by radical surgery as an alternative treatment modality, especially in countries where radiation sources are not available and in patients who desire fertility-sparing procedures despite larger cervical tumor size [111]. The International Atomic Energy Association (IAEA) reports that at least 30 developing countries, including 15 in Africa, do not possess even a single radiation therapy machine. Park et al (2004), in a phase II trial of paclitaxel and cisplatin each at 60 mg/m² every 10 days for three cycles, achieved down-staging in 72% of patients with an objective response [112]. Out of the 43 patients with IB2 to IIB disease, all underwent surgery. Overall 2- and 5-year survival was 94.5% and 89.2%, respectively [113]. Other data suggest that older patients may not achieve comparable outcomes and that surgical morbidity is not inconsequential for patients with advanced disease who are treated with this approach [114]. Among eighteen patients diagnosed with FIGO stage IVA cervical cancer who were treated with paclitaxel 175 mg/m² and cisplatin 75 mg/m² every 21 days for three courses, there was a 66% response rate, and only 55% responded adequately enough to undergo radical surgery (i.e., no peritoneal involvement or widely metastatic disease to lymph nodes) [115]. Of patients who underwent surgery, median surgical time was 7 hours with a median blood loss of 750 mL and median hospitalization of 13.5 days.

A Cochrane review of 18 trials and 2074 patients highlighted the importance of chemotherapeutic dosing characteristics on outcome in patients who receive neoadjuvant chemotherapy compared to radiotherapy alone [116]. A survival disadvantage was observed for patients who received neoadjuvant chemotherapy if a cisplatin dose intensity < 25 mg/m² (HR = 1.35, 95% CI = 1.11 to 1.14, p = 0.002) or a cycle length > 14 days was applied (HR = 1.25, 95% CI = 1.07 to 1.46, p = 0.005); in contrast, neoadjuvant chemotherapy resulted in favorable outcomes if cycle lengths < 14 days (HR = 0.83, 95% CI = 0.69 to 1.00, p = 0.046). In another Cochrane review of six trials including 1072 women comparing neoadjuvant chemotherapy followed by surgery versus radical surgery alone for

early-stage disease, progression-free survival was significantly improved with neoadjuvant chemotherapy (HR = 0.76, 95% CI = 0.62 to 0.94, $p = 0.01$), but no overall survival benefit was observed (HR = 0.85, 95% CI = 0.67 to 1.07, $p = 0.17$) [117]. Phase III trials regarding the use of neoadjuvant chemotherapy in treatment of cervical cancers are limited. The EORTC is conducting a large trial to randomize patients with IB2 to IIB cervical cancer to either cisplatin neoadjuvant chemotherapy followed by radical hysterectomy or external beam radiation with cisplatin. The results are expected by 2018.

Although phase III trials are lacking, use of neoadjuvant chemotherapy is still attractive for patients who desire fertility. Up to 42% of cervical cancers are diagnosed in women < 45 years of age [118]. Traditionally, appropriate candidates for fertility-sparing procedures have been those with IA1 disease, IA2 disease, or IB1 lesions < 2 cm with limited endocervical extension in women younger than 40 years with no nodal involvement. There has been considerable interest in use of neoadjuvant chemotherapy to allow fertility-sparing procedures in women who do not meet these criteria.

The success of taxanes in the treatment of squamous cell carcinomas has led to studies investigating the potential use of the microtubule inhibitor in these patients. Plante et al (2006) were among the first to report use of neoadjuvant chemotherapy for 3 cycles using cisplatin 75 mg/m², paclitaxel 175 mg/m² and ifosfamide 5 g/m² followed by pelvic lymphadenectomy and radical vaginal trachelectomy in patients with bulky IB1 lesions [119]. In this case series, all 3 women had a complete pathologic response. Maneo et al (2008) subsequently described outcomes in 21 patients with IB1 disease who received 3 cycles of the same regimen (or epirubicin 80 mg/m² in place of ifosfamide in adenocarcinoma) then underwent conization; no recurrences were documented after a median follow-up of 69 months and there were 10 pregnancies resulting in 9 live births [120]. Thirty-eight percent of patients entered the study with lesions >2 cm. Similarly, Landoni et al (2007) applied this approach in 2 cases of IB1 disease with tumor >2 cm resulting in no recurrences at a median follow-up of 20 months [121]. Marchiolo et al (2011) used the same neoadjuvant paclitaxel containing regimen for 3–4 cycles in 7 patients with tumors 3–4.5 cm. After treatment they then underwent pelvic lymphadenectomy with radical vaginal trachelectomy [122]. At a median follow-up of 22 months, there was 1 pregnancy and no recurrences were documented. However, one patient eventually required brachytherapy for parametrial disease. Gottschalk et al (2011) described a successful outcome using neoadjuvant paclitaxel 200 mg/m² and cisplatin 100 mg/m² in conjunction with goserelin followed by radical vaginal trachelectomy for a 3.6 cm lesion [123]. These data suggest that treatment with paclitaxel may allow for fertility-sparing surgery in patients with desired fertility.

Trials of non taxane containing regimens have been less successful in achieving the same durability of response. Robova et al (2011) administered 3 cycles of cisplatin 75 mg/m² and ifosfamide 5 g/m² without paclitaxel in dose-dense fashion over a 10-day period to 15 patients with IB tumors prior to pelvic lymphadenectomy and trachelectomy [124]. One patient required radical hysterectomy for nodal involvement. Overall, outcomes with this regimen were less favorable than previous trials with taxanes. At the time of publication, there were three recurrences: 1 patient died of disseminated disease first detected 6 weeks

after delivery, 1 patient with endocervical recurrence underwent cesarean hysterectomy at 38 weeks with radiation therapy, and 1 patient with ectocervical disease underwent radiation therapy after ovarian transposition. Notably, more encouraging case reports have been published using neoadjuvant cisplatin, bleomycin, vincristine and mitomycin C or cisplatin and bleomycin, however, data are limited with these regimens [125]. Neoadjuvant paclitaxel containing regimens have shown the most promise in treating patients with locally advanced cervical cancer who desire fertility sparing surgery or are not candidates for surgery at the time of diagnosis.

Recurrent Disease

The greatest role for taxane chemotherapy lies in the treatment of recurrent disease. While the rate of recurrence for stage IB-IIA disease is only 10–20%, recurrence rates for stage IIB-IVA are as high 50–70% [126]. One-year survival rates for patients diagnosed with recurrent disease remain a dismal 15–20%. Low survival rates have led to studies using a number of chemotherapeutic agents for the treatment of recurrent disease.

Cisplatin has long been regarded as one of the most active agents in the treatment of cervical cancers, with overall response rates as high as 40% in chemo-naïve populations and 17–21% in previously treated populations [127, 128]. Cisplatin 50 mg/m² every 3 weeks by IV infusion had remained the standard for many decades, yielding a progression-free survival of 3 to 5 months, and overall survival of approximately 6 months. Grade 3–4 toxicities may be encountered, and are more common in Caucasian compared to African American women [129].

Paclitaxel, as a single-agent, has been studied at a variety of dosing schemes and has important applications for patients who have received prior platinum therapy. At 170 mg/m² (135 mg/m² in those with prior pelvic radiation) and 250 mg/m² with granulocyte colony-stimulating factor support every 3 weeks, response rates of 17–25% were achieved [130, 131]. Paclitaxel appears to have significant activity in non-squamous histologies. A study of 42 patients with advanced disease, many of whom failed radiation, received paclitaxel at 170 mg/m² (135 mg/m² in those with prior pelvic radiation). There were 4 complete responses and 9 partial responses for an overall response rate of 31% [132]. As a result of this and many other studies, different forms of paclitaxel have been and are currently being studied in the treatment of recurrent cervical cancer.

Nanoparticle albumin-bound paclitaxel (nab-paclitaxel; Abraxane®) may offer several advantages over traditional formulations of paclitaxel suspended in Cremophor. In breast cancer, it has been shown to increase response rates, prolong time to progression, and improve survival [133], presumably due to increased bioavailability and intra-tumoral concentrations [134]. Furthermore, it is an option for patients with hypersensitivity to paclitaxel. In GOG 127V, 35 patients with drug-resistant cervical cancer received nab-paclitaxel 125 mg/m² on days 1, 8 and 15 every 28 days [135]. A 28.6% objective response and 42.9% disease stabilization rate were observed. Docetaxel appears to be much less active compared to both paclitaxel and nab paclitaxel. At 100 mg/m² every 3 weeks response rates of 8.7–13% have been observed; at 35 mg/m² weekly $\times$ 3 weeks of a 28-day

cycle, only disease stabilization could be achieved [136]. Response rates for other single-agents are compared to taxanes in Table 1.

The overall response rates of recurrent cervical cancer are still well below the reported response rates of many recurrent gynecologic cancers. While single-agent paclitaxel and Abraxane have shown the most promise in treating recurrence, studies combining taxanes with other chemotherapeutic drugs were designed in an attempt to improve response rates.

Many of these studies have included platinum-based doublets. During two different phase II trials paclitaxel was given at 135 mg/m² day 1 with cisplatin 75 mg/m² day 2 every 3 weeks. Response rates in both studies were approximately 46% response and overall survival was 7–10 months [170, 171]. Trials were also performed with higher dosages of paclitaxel (175 mg/m²) but did not significantly improve response rate (47%) or overall survival (9 months) [172]. When paclitaxel is given in weekly fashion at 80 mg/m² with carboplatin AUC 2, lower response rates are achieved (20% among 15 advanced or recurrent cervical cancers) [173]. These phase II studies laid the foundation for several phase III trials. Data from GOG-169 suggested the combination of cisplatin 50 mg/m² with paclitaxel 135 mg/m² day 1 every 3 weeks improved response rate (35% versus 19%) and progression free survival (4.8 versus 2.8) but not overall survival (9.7 versus 8.8 months) relative to cisplatin alone [174]. In GOG-204, 513 patients were randomized to receive every three weeks cisplatin 50 mg/m² plus either paclitaxel 135 mg/m² over 24 hours day 1, vinorelbine 30 mg/m² days 1 and 8, gemcitabine 1,000 mg/m² day 1 and 8, or topotecan 0.75 mg/m² days 1, 2, and 3 [175]. There were no differences in response rate (29.1%, 25.9%, 22.3%, and 23.4%, respectively), overall survival (HR 1.15, 95% CI 0.79 to 1.67; HR 1.32, 95% CI 0.91 to 1.92, and HR 1.26, 95% CI 0.86 to 1.82, respectively), or progression-free survival (HR 1.36, 95% CI 0.97 to 1.90; HR 1.39, 95% CI 0.99 to 1.96; HR 1.27, 95% CI 0.90 to 1.78). The authors concluded that the regimens were equivalent but that the trend towards improved survival with cisplatin and paclitaxel (12.9 months versus 10–10.3 months) should be strongly considered in treatment planning.

Substitution of carboplatin AUC 5–6 for cisplatin was shown to produce response rates of 40–53% when given with paclitaxel at 155–175 mg/m² every 3 or 4 weeks in several phase II studies [176, 177]. Subsequently, in the Japanese Clinical Oncology Group (JCOG) trial 0505, 253 patients with no more than one prior platinum-containing regimen and no prior taxane exposure were randomized to either a 24-hour infusion of paclitaxel 135 mg/m² day 1 plus cisplatin 50 mg/m² day 2 or paclitaxel 175 mg/m² with carboplatin AUC 5 day 1 for maximum of 6 cycles every 21 days [178, 179]. There were no differences in overall survival (18.3 versus 17.5 months, $p=0.032$) or progression-free survival (6.9 versus 6.2 months, HR 1.04, 95% CI 0.8–1.35), making the less toxic combination of carboplatin and paclitaxel a potential new standard of care.

Docetaxel used as a single-agent showed response rates in the 0–13% range in previous studies. Despite this poor activity as a single-agent, docetaxel at 60–80 mg/m² combined with carboplatin AUC 6 achieved response rates of as high as 76% in previously untreated patients and 25% in the recurrent setting [180].

Paclitaxel has also been studied in combination with many other drugs doublets. It has been studied as an adjunct to ifosfamide/cisplatin and carboplatin/5-FU [181]. Mountzios et al (2009) randomized 153 patients to either ifosfamide 1.5 g/m² daily for 3 days and cisplatin 70 mg/m² day 2 with or without paclitaxel 175 mg/m² [182, 183]. Addition of paclitaxel resulted in a higher response rate (59% versus 33%, $p = 0.002$), median progression-free survival (7.9 versus 6.3 months, $p = 0.002$), and overall survival (15.4 versus 13.2 months, $p = 0.046$) [184]. Zanetta et al (1999) reported a 67% response rate among 45 patients who received paclitaxel 175 mg/m², ifosfamide 5 g/m², and cisplatin 75 mg/m² (50 mg/m² in irradiated patients) [182]. Choi et al (2006) showed a response rate of 46.7% using the same regimen with paclitaxel at 135 mg/m² [183]. Phase III trials are lacking data to demonstrate the superiority of paclitaxel-containing triplet regimens over doublet therapy. So far taxanes have not been part of any investigations of active quartets.

With relatively poor survival following recurrence, newer targeted therapies have been implemented in the treatment of cervical cancer. Targeted therapies have broadened treatment options for advanced or recurrent cervical cancers. In GOG-227C, 46 patients with recurrent cervical cancer and measurable disease received bevacizumab at 15 mg/kg every 3 weeks [185]. The partial response rate was 11%, with a median duration of response that exceeded 6 months. Progression-free and overall survival was 3.4 and 7.3 months, respectively. These results led to an ongoing phase III study investigating benefit gained from addition of bevacizumab to active doublets. The preliminary results of GOG-240 were presented in June 2013 [186]. Among 452 chemotherapy-naïve patients with persistent, recurrent, or metastatic cervical cancer, there were no differences in patients treated with cisplatin 50 mg/m² plus paclitaxel 135–175 mg/m² day 1 versus topotecan 0.75 mg/m² days 1–3 plus paclitaxel 175 mg/m² day 1 of a 21-day cycle. Addition of bevacizumab to either regimen, however, produced more overall responses (48% versus 36%, $p=0.0078$ and a 4-month increase in overall survival (17 months versus 13 months, HR 0.71, 1-sided $p=0.0035$). These data are encouraging and provide hope that the use of paclitaxel in combination with newer cytotoxic and molecularly targeted regimens could help improve overall survival.

Overall Conclusions

Taxanes are well tolerated and widely active across a spectrum of early and advanced stage gynecologic malignancies. The molecular structures of taxanes are being modified in an attempt to improve the treatment of resistant tumors. They are also being studied in order to develop treatment regimens that will combine taxanes with new biological agents (see manuscript this volume). The use of taxanes and other cytotoxic agents in conjunction with molecularly targeted therapy will likely continue to improve survival in patients with gynecologic malignancies. Taxanes will remain a part of the treatment of gynecologic cancers for the foreseeable future.

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Table 1

Comparison of overall response rates between taxanes and non-taxane agents in recurrent cervical cancer.

	DRUG	RESPONSE RATE (%)	SOURCE
TAXANES	Paclitaxel	17–33%	[130, 131, 137]
	Nab-paclitaxel	28.6%	[135]
	Docetaxel	0–13%	[136, 138, 139]
NON-TAXANES	Ifosfamide	11.1–49.9%	[140–143]
	Vindesine	30%	[144]
	Taniposide	22%	[145]
	Doxorubicin	19.7%	[146]
	Pirarubicin	19%	[147]
	Vinorelbine	17–18.2%	[148, 149]
	Methotrexate	16–17%	[150, 151]
	Etoposide	9.1–11.8%	[149, 152]
	Gemcitabine	8.4%	[153]
	Mitoxantrone	8.0%	[154]
	Cyclophosphamide	7–20%	[155, 156]
	5-FU	4.2–9.6%	[157–159]
	Epirubicin	4%	[160]
	Irinotecan	0–21%	[161–163]
	Vinblastine	0–10%	[164, 165]
	Esorubicin, Irarubicin	0%	[166, 167]
	Vincristine	0%	[168]
	Edatrexate	0%	[169]