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REVIEW ARTICLE

Risk factors and adjuvant chemotherapy in the treatment of endometrial cancer

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Summary

Endometrial carcinoma is the most common and potentially curable gynecologic malignant neoplasm. The staging of endometrial cancer, according to the International Federation of Gynecology and Obstetrics (FIGO), is surgical. Recent studies suggest a therapeutic benefit associated with extensive retroperitoneal lymph node evaluation to determine the disease extent and thereby more effectively direct potentially life-saving adjuvant therapy. Due to the increasing number of endometrial cancer patients who undergo surgical staging, some independent prognostic factors have been identified in early stages (stage I-II), including lymph-vascular space involvement, histologic grade 3, aggressive histologic subtypes (uterine papillary serous carcinoma, clear cell carcinoma), depth of myometrial invasion, cervical invasion and the age of patients. Adjuvant radiation therapy, known to offer survival benefit in advanced-stage disease, may also offer survival benefit in intermediate-risk surgical stage I, but this is followed by a significant risk of serious complications. Based on randomized clinical trials, this review identified that only a limited body of evidence is available which can help clinicians make decisions about adjuvant chemotherapy of patients with high-risk stage I and II, as well as stage IIIA endometrial cancer. Further investigations are required to define the subgroup of patients who benefit from postoperative adjuvant chemotherapy. In addition, the optimal regimen remains to be defined as all of them (doxorubicin/cisplatin - AP, cyclophosphamide/doxorubicin/cisplatin - CAP, paclitaxel/carboplatin - TC, paclitaxel/doxorubicin/cisplatin - TAP) cause significant toxicity. Thereby, combination of carboplatin plus paclitaxel represents an efficacious, low-toxicity regimen for managing intermediate-risk surgical stage I, as well as advanced or recurrent endometrial cancer.

Key words: adjuvant chemotherapy, carboplatin, doxorubicin, endometrial cancer, paclitaxel, risk factors

Introduction

In developed countries, endometrial cancer is the most common malignancy of the female reproductive tract, the 4th most common malignancy in women, and accounts for 6% of all cancers in females [1]. There were approximately 200,000 cases of endometrial adenocarcinoma worldwide with about 50 000 deaths in 2002 [1]. There is, however, wide geographical variation in disease incidence with the highest in North America (22.0 per 100,000 per year) and Europe (11.8-12.5 per 100,000 per year) [1]. Women usually present with peri- or postmenopausal bleeding as their only presenting complaint and this fortunately leads to early diagnosis of the majority of the cases. To date there is no consensus on the utility of screening procedures for early detection of endometrial cancer. Following the revision of the FIGO staging system in 1988 [2], surgery became the recommended treatment for patients with early endometrial cancer, allowing the possibility of surgical staging. FIGO surgical stage is considered the most important independent prognostic indicator of progression-free or overall survival, and has a significant impact on treatment decisions. Fortunately, the majority of patients are diagnosed at an early stage, without clinical evidence of extrauterine spread (FIGO stage I and II), so the prognosis is generally favorable. Five-year survival for women with surgical stage I disease

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ranges from 85 to 90%, stage II from 74 to 83%, stage III from 57 to 66%, and stage IV from 20 to 25% [3].

Once endometrial adenocarcinoma is identified by uterine biopsy, the treatment is total abdominal hysterectomy and bilateral salpingo-oophorectomy. Women with certain histological subtypes, high-grade lesions, deep myometrial invasion, tumor extending to the cervix or ovaries, positive peritoneal cytology, spread to lymphatic or blood vessels or outside the uterus are at high risk of recurrence and may be offered adjuvant radiotherapy [4]. However, the use of radiation therapy for FIGO stages IB, IC and II still remains controversial. Three randomized trials have shown that postoperative radiation therapy decreases the risk of locoregional recurrence, but does not improve the overall survival rate [5-7]. Furthermore, radiation therapy is followed by a significant increased risk of serious complications when compared to surgery alone and is not indicated in women under 60 years and those with grade 2 superficially invasive tumors. Nevertheless, Naumann et al. [8] have reported that most gynecologic oncologists continue to recommend radiation therapy for stage IC or grade 3 endometrial cancers. Jolly et al. [9] reported that vaginal brachytherapy alone has similar overall survival and cumulative recurrence rates to standard external pelvic radiotherapy with the benefit of much lower toxicity rates and shorter duration of treatment in stage I-II endometrial cancer. Analyses of those studies are limited because complete surgical staging was not an entry requirement and the actual number of women with FIGO stage I endometrial adenocarcinoma remained unclear.

There are relatively few reports dealing with postoperative adjuvant chemotherapy for the treatment of patients with early-stage endometrial cancer with risk factors [10-12].

In order to examine the current evidence regarding the use of chemotherapy in stages I, II and IIIA of endometrial cancer, we conducted a search of the literature to identify all relevant articles. The aim of our search was to discuss the evidence available at the present time from the literature regarding the risk factors for relapse and chemotherapy in the adjuvant setting.

High-risk stage I and II endometrial cancer

Endometrial carcinoma is made up of a biologically and histopathologically diverse group of neoplasms that are characterized by a different pathogenesis [13-15]. Estrogen-dependent tumors (type I) are low grade and frequently associated with endometrial hyperplasias, in particular atypical hyperplasia. Unopposed estrogenic stimulation is the driving force behind this group of tumors. It may be the result of anovulatory cycles that occur in young women with the polycystic ovary syndrome or due to normally occurring anovulatory cycles at the time of menopause. The iatrogenic use of unopposed estrogens as hormone replacement therapy in older women also is a predisposing factor for the development of endometrial cancer. The second type (type II) of endometrial cancer appears less related to sustained estrogen stimulation. Endometrial papillary serous carcinoma and clear cell carcinoma comprise the vast majority of type II endometrial cancers [13-15]. These cancers, unlike type I cancers, are characterized by a high recurrence rate and poor prognosis [13-15]. The distribution of histologic subtypes of endometrial carcinoma is shown in Table 1.

Due to the increasing number of endometrial cancer patients undergoing surgical staging, some independent prognostic factors (risk factors for relapse) have been identified in early (FIGO I-II) stages, including depth of myometrial invasion, cervical involvement, histologic grade 3, lymph-vascular space involvement, and aggressive histologic types (papillary serous carcinoma and clear cell carcinoma) (Table 2) [13-15].

The depth of myometrial invasion has been demonstrated to be a strong predictor of prognosis in patients with stage I and II endometrial cancer [11,13,14].

Cancer extending to the cervix tends to be of high grade and deeply invasive into the myometrium [14].

Histologic grade 3 is the most relevant independent prognostic factor in patients with endometrial cancer confined to the uterus [12].

Table 1. Distribution of histologic subtypes of endometrial carcinoma [13,14]

Endometrial carcinoma subtype	*%*
Endometrioid adenocarcinoma and variants	80-85
Variant with squamous differentiation	
Villoglandular	
Secretory variant	
Ciliated cell variant	
Mucinous adenocarcinoma	1-9
Serous adenocarcinoma	1-10
Clear cell carcinoma	1-6
Mixed cell carcinoma	NR
Squamous cell carcinoma	0.1
Transitional cell carcinoma	Rare
Small cell carcinoma	>1
Undifferentiated carcinoma	1-2
Others	Rare

NR: not recorded

Table 2. Risk factors for relapse of endometrial carcinoma in stage I and II

Risk factor	*References*
Depth of myometrial invasion	Aioki et al. [11], Silverberg et al. [13], Ronnett et al. [14]
Cervical involvement	Aioki et al. [11], Silverberg et al. [13], Ronnett et al. [14]
Histologic grade 3	Aioki et al. [11], Kodoma et al. [12], Silverberg et al. [13], Ronnett et al. [14]
Lymph-vascular space involvement	Aioki et al. [11], Silverberg et al. [13], Ronnett et al. [14], Rose [15]
Aggressive histologic subtypes (papillary serous + clear cell)	Silverberg et al. [13], Ronnett et al. [14], Rose [15], Goff [19], Podratz et al. [20]

Hirai et al. [10] assessed the efficacy of adjuvant chemotherapy in stage I endometrial carcinoma with lymph-vascular space invasion. In 54 patients, they reported statistically significant differences between the survival rates of patients who had surgery followed by adjuvant chemotherapy and patients who had surgery alone. Aoki et al. [11] defined subgroups of patients with stage I and II endometrial carcinomas that benefited from postoperative chemotherapy (CAP regimen). These patients were divided into low- and high-risk groups based on a score system of the prognostic factors (histologic grade 3, invasion of the outer half of the myometrium, lymph-vascular space invasion and cervical invasion). Among high-risk group patients, 5-year disease-free and 5-year overall survival rates were significantly better in patients treated with adjuvant chemotherapy [12].

Endometrial papillary serous carcinoma is an aggressive histologic type of endometrial cancer which was first reported in 1981 by Lauchlan [16]. The next year Hendrickson and co-workers [17] reported that although papillary serous carcinoma accounted for only 3-5% of endometrial cancers, it represented more than 50% of the recurrences in women with disease thought to be confined to the uterus. Other authors announced that papillary serous carcinoma represents 3-10% of all endometrial cancers, but accounts for 25% of the disease mortality [15,18]. Microscopically, it is characterized by complex papillary architecture, marked nuclear atypia, and irregular epithelial tufting. Biologically, papillary serous carcinoma is an extremely aggressive tumor, with a propensity for lymph-vascular space invasion, myometrial invasion, and extrauterine spread [19]. Even patients with disease confined to the endometrium may have microscopic evidence of extrapelvic metastases. At the time of presentation, 70-87% of women with papillary serous carcinoma will have disease outside the uterus, in contrast to only 15-20% of women with endometrioid adenocarcinoma having metastatic disease at presentation [19,20]. Therefore, thorough surgical staging including omentectomy, pelvic and paraaortic lymphadenectomy, multiple biopsies of the upper abdomen, and saline washings of the pelvic and paracolic spaces should be carried out in patients with this disease variant [18,21]. Surgical staging reduces the risk of including occult stage III and IV patients into stage I disease, which has been a significant problem with many earlier studies.

Five-year survival rates for papillary serous carcinoma vary from 30 to 80% in patients with stage I-II disease and from 0 to 25% in patients with stage III-IV disease, both significantly lower than those reported in other subtypes of endometrial carcinoma [7,18,22,23]. There are additional significant differences between endometrioid carcinoma and papillary serous carcinoma. Women with papillary serous carcinoma tend to be older (median age 65-70), nonobese and parous [19]. Atypical hyperplasia is not a precursor lesion for this disease. Uterine papillary serous carcinoma is not associated with estrogen excess, it usually does not express estrogen (ER) or progesterone receptors (PR), but it frequently bears p53 mutations and high degrees of aneuploidy. In contrast to endometrioid adenocarcinoma, microsatellite instability, k-RAS and PTEN mutations are uncommon in papillary serous carcinoma [24].

While much has been learned from retrospective studies regarding pathology and surgical management for papillary serous carcinoma, the optimal adjuvant treatment, particularly in stage I and II disease, is unclear and no consensus on how to treat these patients has been reached. Treatment recommendations have included observation, whole abdominal radiation, pelvic radiation, vaginal cuff radiation, intraperitoneal chemotherapy, intravenous chemotherapy and combinations of these modalities. Most of these studies have been retrospective chart reviews with small numbers of patients treated in such a heterogeneous manner that it has been difficult to draw meaningful conclusions.

Patients with stage IA uterine papillary serous carcinoma may benefit from concomitant platinum-based chemotherapy and brachytherapy (referred to as chemoirradiation) [18,25].

Because papillary serous carcinoma spreads over the peritoneal surfaces like ovarian carcinoma, and

therefore often presents at a more advanced stage at diagnosis than other uterine carcinomas [17], there have been many attempts to treat this disease with chemotherapy. Initial studies in the setting of measurable disease with single-agent chemotherapy (cyclophosphamide, doxorubicin, cisplatin) resulted in response rates of only 15-20%. In more recent GOG (Gynecology Oncology Group) studies, response rates of papillary serous carcinoma to doxorubicin/cisplatin were 42%, to doxorubicin/paclitaxel 37% and to doxorubicin/paclitaxel/cisplatin 50% [26]. None of 3 recent studies addressing the role of adjuvant therapy in surgical stage I uterine papillary serous carcinoma patients found that chemotherapy was effective [27-29], in contrast to the study of Kelly and co-workers [18] whose results highlighted the effectiveness of adjuvant platinum-based chemotherapy (paclitaxel 175 mg/m^2 and carboplatin AUC 5) and vaginal brachytherapy in treating stage I uterine papillary serous carcinoma. Those results are consistent with other recent studies which indicate that platinum- and taxane-based regimens may be an appropriate approach for the adjuvant treatment of high risk endometrial cancers [30-32].

In summary, the data on adjuvant chemotherapy for stage I uterine papillary serous carcinoma are limited, and the available studies are generally under-powered to assess if chemotherapy improves survival and which chemotherapeutic regimen is the most beneficial.

Adjuvant chemotherapy in stage IIIA endometrial cancer

FIGO stage IIIA endometrial cancer includes a heterogeneous population of patients whose disease has metastasized to the uterine serosa, fallopian tubes and ovaries or with positive peritoneal cytology. This stage comprises two intuitively separate groups: those with histological proof of disease in tissue outside the uterus (IIIA2) and those with positive peritoneal cytology alone (IIIA1). While extrauterine spread is a well recognized poor prognostic factor in endometrial cancer, the clinical significance of malignant cells identified by cytology of peritoneal washings is unclear. Some studies have suggested that positive cytology has no association with survival [33-35], while others have observed worse outcomes for patients with positive cytology, even when controlling for other prognostic factors [36-39].

Patients with stage IIIA disease are usually considered candidates for aggressive adjuvant therapies, including combination chemotherapy and radiotherapy. Analysis of patterns of recurrence shed light on the appropriateness of systemic vs. local adjuvant treatment. Havrilesky et al. [39] noted that 61% of the recurrences were outside the pelvis, compared to 29% local recurrences. This is similar to the findings of Mariani et al. [14] (88% of all recurrences were distant). Now, there is increasing evidence that patients with stage IIIA disease are at risk for recurrence at sites not amenable to standard pelvic external beam radiotherapy. A recently published randomized controlled trial suggests that adjuvant combination chemotherapy is superior to whole abdominal radiotherapy in the treatment of all patients with stage III endometrial cancer [32].

Chemotherapy regimens

There is no standard adjuvant chemotherapy regimen for patients with endometrial cancer. From a historical perspective, several agents have been demonstrated to have antitumor activity (Table 3) [40-44]. Characteristics of phase II trials of combination chemotherapy and randomized controlled trials for advanced endometrial cancer are shown in Table 4 [45-53] and Table 5 [54-60]. Doxorubicin with or without cisplatin has been used by most clinicians as the preferred cytotoxic chemotherapy for the treatment of this disease, although substituting carboplatin for cisplatin may improve tolerability without sacrificing efficacy [61]. Myelosuppression may be more frequent but nephrotoxicity, neurotoxicity and emesis were less fre-

Table 3. Characteristics of phase II trials of single-agent chemotherapy for advanced disease

Authors [reference]	*Number of patients*	*Chemotherapy*	*Overall response (%)*	*Median PFS (months)*	*Median OS (months)*
Thigpen et al. [40]	55	Doxorubicin 60 mg/m^2 i.v./3 weeks	37	NR	6.8
Thigpen et al. [41]	56	Cisplatin 50 mg/m^2 i.v./3 weeks	20	2.9	8.2
Long et al. [42]	25	Carboplatin 400 mg/m^2 i.v./3 weeks	28	3.8	7.1
Calero et al. [43]	27	Epirubicin 80 mg/m^2 i.v./3 weeks	26	6.0	9.5
Ball et al. [44]	30	Paclitaxel 250 mg/m^2 i.v./3 weeks	36	3.8	9.5

PFS: progression free survival, OS: overall survival, i.v.: intravenous administration, NR: not recorded

Table 4. Phase II trials of combination chemotherapy for advanced disease

Authors [reference]	*Number of patients*	*Chemotherapy*	*Overall response (%)*	*Median PFS (months)*	*Median OS (months)*
Barrett et al. [45]	33	Cisplatin 60 mg/m^2, doxorubicin 60 mg/m^2 i.v./3 weeks	60	7.5	14
Trope et al. [46]	19	Cisplatin 50 mg/m^2, doxorubicin 50 mg/m^2 i.v./3 weeks	60	NR	NR
Hancock et al. [47]	18	Cisplatin 50 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2 i.v./3 weeks	56	NR	NR
Burke al. [48]	102	Cisplatin 50 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2 i.v./3 weeks	45	NR	NR
Long et al. [49]	30	Cisplatin 70 mg/m^2, doxorubicin 40 mg/m^2, vinblastine 9 mg/m^2, methotrexate 90 mg/m^2 i.v./3 weeks	67	7.2	9.9
Lissoni et al. [50]	30	Cisplatin 50 mg/m^2, epirubicin 70 mg/m^2, paclitaxel 175 mg/m^2 i.v./3 weeks	73	NR	NR
Dimopoulos et al. [51]	24	Cisplatin 75 mg/m^2, paclitaxel 175 mg/m^2 i.v./3 weeks	67	8.4	17.6
Hoskins et al. [52]	67	Carboplatin AUC 5-7, paclitaxel 175 mg/m^2 i.v./3 weeks	61	NR	15-26
Deppe et al. [53]	29	Doxorubicin 40 mg/m^2, 5-FU 400 mg/m^2, cyclophosphamide 400 mg/m^2 i.v./3 weeks, megace 160 mg/day	45	NR	6.7-12.5

PFS: progression free survival, OS: overall survival, i.v.: intravenous administration, AUC: area under the curve, NR: not recorded

quent and milder with carboplatin compared with cisplatin-based regimens.

Cyclophosphamide/adriamycin/cisplatin (CAP) regimen was commonly used too as adjuvant chemotherapy, as well as in advanced disease [62].

Recently, newer agents such as paclitaxel have shown promising response rates and improved survival in endometrial cancer patients [63]. Paclitaxel has been associated with favorable response rates either as a single agent or in combination with platinum-based

Table 5. Randomized controlled trials of chemotherapy for advanced disease

Authors [reference]	*Patients randomly assigned (excluded)*	*Chemotherapy*	*Overall response (%)*	*Median PFS (months)*	*Median OS (months)*
Horton et al. [54]	47 (7)	Arm 1: doxorubicin 50 mg/m^2 i.v./3 weeks Arm 2: cyclophosphamide 666 mg/m^2 i.v./ 3 weeks until progression	19 0	NR	NR
Edmondson et al. [55]	30 (0)	Arm 1: cisplatin 60 mg/m^2 i.v./3 weeks Arm 2: doxorubicin 40 mg/m^2, cisplatin 40 mg/m^2, cyclophosphamide 400 mg/m^2 i.v./4 weeks until progression	21 31	1.8 2.9	4.1 6.6
Thigpen et al. [56]	387 (111)	Arm 1: doxorubicin 60 mg/m^2 i.v./3 weeks Arm 2: cyclophosphamide 500 mg/m^2, doxorubicin 60 mg/m^2 i.v./3 weeks	22 30	3.2 3.9	6.9 7.3
Aapro et al. [57]	177 (12)	Arm 1: doxorubicin 60 mg/m^2 i.v./4 weeks Arm 2: doxorubicin 60 mg/m^2, cisplatin 50 mg/m^2 i.v./4 weeks	17 43	7 8	7 9
Gallion et al. [58]	352 (10)	Arm 1: doxorubicin 60 mg/m^2, cisplatin 60 mg/m^2, i.v./3 weeks, for 8 cycles Arm 2: doxorubicin 60 mg/m^2, cisplatin 60 mg/m^2, i.v. at 6 am /3 weeks, for 8 cycles	46 49	6.5 5.9	11.2 13.2
Thigpen et al. [59]	299 (18)	Arm 1: doxorubicin 60 mg/m^2 i.v./3 weeks Arm 2: doxorubicin 60 mg/m^2, cisplatin 50 mg/m^2 i.v./3 weeks	25 42	NR NR	NR NR
Fleming et al. [60]	273 (10)	Arm 1: doxorubicin 60 mg/m^2, cisplatin 50 mg/m^2 i.v./3 weeks, for 7 cycles Arm 2: doxorubicin 45 mg/m^2, cisplatin 50 mg/m^2, paclitaxel 160 mg/m^2 i.v./3 weeks, for 7 cycles, plus G-CSF support	34 57	5.3 8.3	12.3 15.3

PFS: progression free survival, OS: overall survival, i.v.: intravenous administration, NR: not recorded, 5-FU: 5-fluorouracil, G-CSF: granulocyte colony stimulating factor

chemotherapy. Zanotti et al. [30] performed a retrospective analysis of 24 uterine papillary serous carcinoma patients treated with platinum-based chemotherapy and paclitaxel in an adjuvant setting or for recurrence. Eight patients had surgical stage I disease. The reported response rate was 89% (8/9) in patients treated for residual disease after initial surgery, and 64% (7/11) for those with recurrent disease, although more specific outcomes for the stage I subgroup were not presented. Rosenberg et al. [64] investigated the use of combination chemotherapy in 8 clinical stage I patients after radical surgery. Pelvic radiotherapy was followed by cisplatin/epirubicin chemotherapy. No recurrences were seen at 32 months of follow-up. Low et al. [65] treated 9 stage I patients with chemotherapy (cisplatin/epirubicin, carboplatin/paclitaxel or gemcitabine/carboplatin) followed by pelvic and/or vaginal brachytherapy. Only 1 recurrence (lung) was reported after a median follow-up of 28 months.

The combination of paclitaxel, adriamycin and carboplatin (TAC) combines the 3 most effective single agents in endometrial cancer with potentially less toxicity than TAP (paclitaxel/doxorubicin/cisplatin). In addition, the regimen was further simplified by delivering all drugs on day 1 of each cycle [66].

Conclusions

Most patients with endometrial cancer present their symptoms early in the disease course, leading to an overall favorable outcome. However, some patients who are in early-stage disease may carry some risk features that would hamper their prognosis. For these early-stage disease cases with high risk of recurrence, radiation therapy certainly plays a major role as an adjuvant treatment. Despite an excellent local disease control by radiation, systemic failures are still encountered. To improve prognosis, other types of adjuvant therapy have been attempted. In this review, adjuvant chemotherapy for early-stage endometrial cancer is discussed.

FIGO surgical stage is considered the most important independent prognostic indicator of progression-free or overall survival, and has a significant impact on treatment decisions. However, some histologic subtypes, like papillary serous carcinoma and clear cell carcinoma, are associated with a high rate of recurrence compared to endometrioid carcinoma after surgical treatment alone. Therefore, the need for effective adjuvant therapy is apparent. However, currently, no randomized data have determined if adjuvant chemotherapy improves the outcome and what is the optimal treatment. Unfortunately, in most published works there is imprecision in the proportion of patients who underwent complete surgical staging, and confusion about what should be considered as complete surgical staging. Some authors believe that complete staging includes standard endometrial staging, but for others, complete staging should also comprise omentectomy and random peritoneal biopsies. Therefore, it is possible that in some reports, occult stage IV may have been included as presumed stage I, leading to underestimation of the efficacy of adjuvant therapy. This paper illustrates that we need appropriately powered, randomized, controlled trials with completely staged patients to determine the optimal adjuvant treatment for uterine papillary serous carcinoma.

Based on the available scientific evidence, we believe that, firstly, patients with uterine papillary serous carcinoma should undergo complete surgical staging, including omentectomy and peritoneal biopsies. Secondly, until the results of large series or randomized controlled trials will be available, we feel that combined radiotherapy (pelvic or vaginal cuff) and chemotherapy (platinum-based and paclitaxel) are justified for all stage I uterine papillary serous carcinoma patients.

A number of drugs have some activity in endometrial cancer. The most commonly investigated drugs include platinums, anthracyclines and taxanes, either alone or in combinations. The patients, however, were selected according to different criteria. Therefore, in the absence of a randomized control group, it is not possible to tell whether any of the combinations is superior in terms of progression-free survival, overall survival or impact on quality of life.

A significant percentage of poorly differentiated tumors, often with serous papillary or clear cell histology, have been found to overexpress the epidermal growth factor type II receptor. Anti-HER-2/neu-targeted therapy might be a novel and attractive therapeutic strategy in patients harboring this biologically aggressive variant of endometrial cancer.

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REVIEW ARTICLE

Chemotherapy and cerebrovascular disease

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Summary

Cerebrovascular disease is common in cancer patients. Some tumors are at high risk for cerebrovascular complications. The development of cerebrovascular disease may be provoked by cancer treatment. No well-planned prospective studies about other causes of thrombosis are available, although various case reports about thrombosis related to chemotherapy have been published. L-asparaginase, cisplatin, 5-fluorouracil (5-FU) and methotrexate are anticancer agents which are reported to relate to stroke. The mechanisms by which antineoplastic agents may lead to stroke include endothelium toxicity and abnormalities of coagulation factors. Also, brain hemorrhages that could result from chemotherapy effects on the hemostatic system were reported. Besides, it is difficult to determine whether stroke is caused by chemotherapy or cancer itself. Clinicians deal not only with problems originating from cancer itself, but also with the complications resulting from its treatment. Treatment-induced cerebrovascular disorders affect quality of life and survival in cancer patients. For this reason, cancer treatment should be planned by taking into consideration the possibility of cerebrovascular complications.

Key words: chemotherapy, coagulopathy, disseminated intravascular coagulation, embolism, intracranial hemorrhage, stroke

Introduction

Cerebrovascular disease is the second most common central nervous system (CNS) pathology in cancer patients, next to metastasis. Cerebrovascular disease manifests in approximately 15% of cancer patients [1]. The most classic and severe clinical form of the disease is hemiplegia accompanied by coma. The least severe clinical form of the disease includes neurological deficiencies too inconspicuous and ambiguous to be dealt medically. Cerebrovascular disease can be considered under two main titles: ischemic and hemorrhagic.

Cancer patients are at risk of stroke due to direct or indirect effects of malignancies. Pressure and blockage by tumor of brain vessels, coagulopathy triggering hemorrhage or thrombosis, and atherosclerosis resulting from treatment, are stroke mechanisms related to cancer [2]. Some tumors have a high risk of cerebrovascular complications. Rarely, cerebrovascular disease may be the first sign of cancer [3]. Table 1 summarises the causes of stroke in cancer patients.

The development of cerebrovascular disease is also provoked by cancer treatment. Radiotherapy and chemotherapy are the two main treatment methods used in cancer therapy. Application of radiotherapy on

Table 1. Etiology and mechanisms of stroke in cancer patients

Etiology	*Mechanisms*
Thrombosis	Coagulopathy
	Vessel compression/infiltration
	Treatment-related
Embolism	Tumor-related
	Septic embolization
	Non-bacterial thrombotic endocarditis
Intracranial hemorrhage	Tumor-related
	Coagulopathy
	Treatment-related

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