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Review paper

The role of chemotherapy in invasive cancer of the cervix uteri: current standards and future prospects

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For many decades, invasive cervical cancer has been considered more or less chemoresistant and chemotherapy has been limited to patients presenting with overt metastatic disease or those suffering from pelvic recurrences which could not be advised to secondary local treatments. However, more than 20 different single agents are considered active in cervical cancer. Recent cooperative clinical trials have demonstrated the superiority of multi-modality strategies for patients with high-risk cervical cancer. These studies integrating chemotherapy as part of the primary therapeutic concept have provided the most significant improvement of locally advanced disease in more than three decades. This review summarizes current standards of chemotherapy for invasive cervical cancer and shows new developments which may improve systemic treatment of the disease. [© 2001 Lippincott Williams & Wilkins.]

Key words: Cervix uteri, chemotherapy, invasive cancer.

Introduction

Invasive cancer of the uterine cervix is the third most common malignancy affecting women worldwide.[1] In most industrialized countries, the prognosis of this disease has improved dramatically during recent decades, which can mostly be attributed to the success of cancer screening by gynecological examination and routine performance of exfoliative cytology. As a result, cervical cancer is frequently detected at a preinvasive or early invasive stage (i.e. FIGO stage Ia–Ib) which is almost curable with local treatments. However, the stage-related prognosis of cervical cancer did not change that much during the same period of time and patients presenting with locally advanced cancer (i.e. FIGO stage IIa–IVa), metastatic or recurrent disease still have a poor chance of cure. Moreover, a number of risk factors have been identified for patients with tumors limited to the cervix indicating a significant adverse impact on cure and survival such as bulky disease, vascular invasion, lymph node involvement, non-squamous histology, incomplete surgical resection or age below 35 years. Recently, a trend towards a higher incidence of these high-risk tumors has been observed in both America and Europe.

Until the late 1990s, radical surgery was considered the treatment of choice in patients with primary stage I (IIa) cervical cancer, whereas combined radiotherapy has been favored in those presenting with more advanced stages limited to the pelvis. In high-risk, early-stage disease, most patients underwent post-operative irradiation. This procedure clearly improved local disease control but had little or no effect on median survival, thus indicating the presence of microscopic distant disease in a substantial number of such patients which can unlikely be controlled by local treatment modalities only.

For many decades invasive cervical cancer has been considered more or less chemoresistant and chemotherapy has been limited to patients presenting with overt metastatic disease or those suffering from pelvic recurrences which could not be advised to secondary local treatments. However, more than 20 different single agents are now considered active in this tumor entity producing response rates of 15% or greater and recent trials will clearly identify additional active drugs. Moreover, it is not surprising that chemotherapy produces little effect in pretreated patients due to relative or absolute drug resistance related to prior therapy. Both radical surgery and

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irradiation are known to deteriorate the local vascularization, thus limiting the effective dose of drugs administered systemically. Moreover, tumor cells living at hypoxic conditions are exposed to intensive genetic stress producing genetic instability, loss of p53 function, dedifferentiation, induction of various molecular mechanisms of drug resistance (i.e. *mdr1* activation or enhanced DNA repair), increased production of vascular endothelial growth factor, higher invasive potential and, finally, acquisition of a more aggressive biological phenotype. It has already been shown that response rates for platinum and other drugs achieved in radiotherapy-naive patients with both pelvic recurrences and distant metastases compare favorably with those seen in patients after local irradiation.[2] As in other tumor types like lung or head and neck cancer, this resulted in the development of multi-modality strategies for patients with high-risk primary cervical cancer integrating chemotherapy as part of the primary therapeutic concept. For various primary therapy scenarios, recent trials demonstrated the superiority of such multi-modality treatments over more conventional therapeutic concepts and this for the first time since many decades has changed the therapeutic standards substantially. The purpose of this review is both to summarize current standards of chemotherapy for invasive cervical cancer and to highlight new developments which may further improve systemic treatment of this important disease.

Active drugs in invasive cervical cancer and treatment of recurrent or overt metastatic disease

Recently, recurrent cervical cancer and metastatic disease has been the best established indication for systemic cytostatic treatment. Although cervical cancer is regarded as being more chemoresistant compared to other gynecologic tumors such as breast or ovarian cancer, more than 20 different single agents have been identified to display significant clinical activity in squamous tumors with response rates of 15% and more (Table 1).[3] Among established drugs, platinum analogs have been most intensively investigated and, particularly, cisplatin is considered the major cytotoxic agent for the treatment of invasive cervical cancer with reported response rates of around 23%. The most accepted dosage of cisplatin is 50 mg/m^2 given at a 3-week schedule. In controlled trials, both higher dosages (i.e. 100 mg/m^2 q3w) or different application schedules failed to improve progression-free or overall survival (Table 2). Among well-studied non-platinum agents, ifosfamide, dibromodulcitol and 5-fluorouracil (5-FU) are those also showing response rates of more than 20%. With the exception of cisplatin, response rates achieved with single-agent chemotherapy in non-squamous tumors are even lower (Table 3).

Table 1. Cytotoxic drugs active against squamous cell carcinoma of the cervix (response rates $\geqslant$15%)

Drug	Patients (*N*)	Response rate (%)
Alkylating agents		
cyclophosphamide	251	15
chlorambucil	44	25
dibromodulcitol	102	23
galacitol	36	19
ifosfamide	157	22
melphalan	20	20
Heavy metal complexes		
cisplatin	815	23
carboplatin	175	15
antibiotics		
doxorubicin	266	17
porfiromycin	78	22
Antimetabolits		
5-FU	142	20
methotrexate	96	18
baker's antifol	32	16
Plant alkaloids		
vincristine	55	18
vindesine	21	24
vinorelbine	35	40
New substances		
paclitaxel	52	17
docetaxel	14	14
topotecan	43	19
irinotecan	142	20
gemcitabine	45	11
hexamethylmelamine	64	19

The last decade has seen a dramatic acceleration of preclinical and clinical drug development, and a number of newer compounds have already shown promising clinical activity in advanced cervical cancer. Among these, the taxanes (paclitaxel, docetaxel), the camptothecin analogs (irinotecan, topotecan), vinorelbin and gemcitabine are the most interesting ones as most of these agents display major radiosensitizing properties (Table 1). In particular, the topoisomerase I poisons irinotecan and topotecan have been found to be active even in patients failing preceding platinum-based chemotherapy.[4]

A variety of different two- to four-drug combination regimens have been studied in numerous trials performed during the last two decades. In these trials,[5–13] platinum has most frequently been combined with ifosfamide, bleomycin, 5-FU, mitomycin C and vinca alkaloids (Table 4). Generally, these combinations produce response rates which normally exceed those seen with single-agent protocols. Pre-

ceding irradiation, however, must be considered a major limitation for all these protocols, significantly reducing the likelihood of clinical response. Combining platinum with one of the afore-mentioned novel agents has produced particularly promising clinical activity. However, most of the data concerning combination chemotherapy are generated in small, non-randomized trials, thus substantially limiting the clinical utility. Correspondingly, four randomized trials[14–17] performed so far failed to demonstrate any survival benefit of different platinum-based combinations compared to single-agent cisplatin given at 50 mg/m^2 every 3 weeks, although mostly showing higher response rates for the combinations (Table 5). It is clearly debatable whether the longer progression-free survival for cisplatin plus ifosfamide versus cisplatin alone seen in the GOG 110 trial really justifies its use as standard front-line therapy in patients with metastatic cervical cancer because the combination was significantly more toxic (e.g. myelosuppression, renal toxicity, peripheral and central neurotoxicity) and did not improve the median overall survival significantly. The recently reported GOG 169 comparing single-agent cisplatin with cisplatin plus paclitaxel provided similar results. As in the previous study, the combination which induced grade 3–4 anemia and neutropenia led to a higher response rate (36.2 versus 19.4%) and a significantly prolonged progression-free survival (2.8 versus 4.8 months). However, the median overall survival remained unchanged (8.8 versus 9.7 months). Therefore, single-agent cisplatin at 50 mg/m^2 should be considered the current standard for the treatment of metastatic cervical cancer unless any other regimen has demonstrated clear superiority in terms of improved survival time. Taking into account the higher risk of adverse effects, the combination of cisplatin and ifosfamide or paclitaxel may be regarded as a therapeutic alternative in situations when rapid symptom control is mandatory.

Table 2. Results of major trials for single-agent therapy with cisplatin

Scheme (cisplatin)	Prior chemotherapy	Patients (*N*)	Response rate (%)
GOG 26C			
50 mg/m^2, 2 h, q3w	no	22	50
	yes	12	16
GOG43			
50 mg/m^2, 2 h, q3w	no	150	21
100 mg/m^2, 2 h, q3w	no	166	31
5 × 20 mg/m^2, 2 h, q3w	no	126	25
GOG64			
50 mg/m^2, 24 h, q3w	no	164	17
	no	156	13

Table 3. Studies of active substances in non-squamous carcinoma of the cervix

Drug	Patients (*N*)	Response rate (%)
Cisplatin	20	20
Piperazinedione	14	14
Etoposide	19	5
Mitoxantrone	25	8
Ifosfamide	24	12
5-FU/leucovorin	43	14

Adjuvant chemotherapy

Metastatic disease in the pelvic lymph nodes is a poor prognostic sign. It has been postulated that metastasis

Table 4. Activity of different combinations of new substances in the treatment of cervical cancer

Regimen	Author	Patients (*N*)	Response rate (%)
CDDP/BLEO	Brenner, 1987; Edmonson, 1988	66	55
CDDP/MMC	Brenner, 1988	130	37
CDDP/CPT-11	Sugiyama, 1998	30	68
CDDP/VBL/BLEO	Friedlander, 1983	66	65
CDDP/DOX/MTX	Fine, 1983; Wheelock, 1985	76	34
CDDP/MMC/VCR/BLEO	Brenner, 1988	103	33
CDDP/MMC/VP-16/BLEO	Chauvergne, 1993	60	58
PCT/CBDCA	Mickiewicz, 2001	32	72
CDDP/IFO	Eifel, 2001	9–30	50–100
CDDP/5-FU	Eifel, 2001	29	69

CBDCA=carboplatin; CDDP=cisplatin; PCT=paclitaxel; MMC=mitomycin C; DOX=doxorubicin; DCT=docetaxel; MTX=metotrexare; CPT=irinotecan; BLEO=bleomycin; VBL=vinorelbine; VCR=vincristine; IFO=ifosfamide.

to pelvic nodes may be associated with lesion size,[18] deep stromal invasion and involvement of capillary or lymphatic vascular spaces.[19] Patients with operable cervical cancer but positive lymph nodes or other risk factors like tumor size 4 cm or greater, lymphangiosis or haemangiosis, infiltration of the parametrium or resection *non in sano* have a significantly higher risk of recurrent disease. Age below 35 years or non-squamous histology has also been attributed to a higher risk of recurrence or death. Postoperative therapy has been advocated in the presence of these prognostic factors or when surgical margins are positive. Postoperative pelvic radiation therapy increases local control, but there are no controlled studies showing improved survival. As in other tumors like breast cancer, the risk of developing distant metastasis might be reduced by systemic adjuvant treatment. A number of non-randomized trials investigating different regimens have demonstrated promising survival periods. A direct comparison of the results obtained with irradiation or postoperative chemotherapy has never been published. Although addition of radiotherapy to adjuvant chemotherapy did not improve survival (Table 6), both these studies[20,21] are unable to define the role of adjuvant chemotherapy in cervical cancer.

Neoadjuvant chemotherapy prior to radiotherapy

In high-risk patients, it is desirable not only to achieve adequate regional control, but also to exert a systemic effect. Looking for new strategies in the treatment of advanced tumor stages (FIGO stage $\geqslant$3B), the administration of chemotherapy before any other

Table 5. Major trials comparing single-agent and platinum-based combinations

Regimen	Patients (*N*)	Response rate (%)	Median survival (month)
Alberts, 1987			
CDDP	9	33 (1 CR, 2 PR)	17.0
CDDP/MMC	51	25 (2 CR, 11 PR)	7.0
CDDP/MMC/VCR/BLEO	54	22 (4 CR, 8 PR)	6.9
Vermorken, 1996			
CDDP	144	19 (8 CR, 20 PR)	9.4
CDDP/MMC/VDS/BLEO	143	31 (11 CR, 33 PR)	10.0
Omura, 1996			
CDDP	146	18 (9 CR, 16 PR)	8.0
CDDP/DBD	153	21 (14 CR, 17 PR)	7.3
CDDP/IFO	155	31 (19 CR, 28 PR)	8.3
Moore, 2001			
CDDP	134	19.4	8.8
CDDP/PCT	130	36.2	9.7

CDDP=cisplatin; DBD=dibromodulcitol; VDS=vindesine; BLEO=bleomycin; MMC=mitomycin C; IFO=ifosfamide; VCR=vincristine; PCT=paclitaxel.

Table 6. Results of phase III trials with or without radiotherapy in the adjuvant treatment of cervical cancer

Regimen	Patients (*N*)	FIGO stage	Risk factors	Survival rates (%)
Curtin, 1995		Ib–IIa	N+, bulky	
CDDP/BLEO	44		disease	80
versus				
CDDP/BLEO+RX	45			78
Tattersall, 1995		Ib–IIa	N+	
CDDP/VBL/BLEO+RX	34			62
versus				
RX	37			70

CDDP=cisplatin; VBL=vinorelbine; BLEO=bleomycin; RX=radiotherapy.

treatment is a theoretical alternative way both to reduce the tumor volume and improve the success of local treatment. The concept of chemotherapy followed by radiotherapy had been developed to allow radiation of the tumor under more favorable conditions. Preoperative chemotherapy, which shows good results in other tumor entities like breast cancer, makes surgical treatment possible in clinically inoperable patients.[22] Many arguments have been used to justify or to question the use of neoadjuvant chemotherapy. Up to now 17 randomized trials on neoadjuvant chemotherapy followed by radiotherapy have demonstrated response rates between 35 and 100%. The lack of a reduced vascularization in the pelvis due to surgery or irradiation favors the response rates of the chemotherapy. It can be stated that all phase III trials evaluating neoadjuvant chemotherapy, using appropriate drugs and doses, obtained good response rates as compared to treatment with radiation alone. However, in most of these trials patients with advanced tumor stages did not show an improved survival (Table 7). Chauvergne *et al.*[23] compared 172 patients with stage IIB and III cervical cancer with and without neoadjuvant chemotherapy consisting of cisplatin 80 mg/m^2, methotrexate, chlorambucil and vincristine. The response rate to chemotherapy was 43%, but no difference was seen in the local clinical response rate and the survival rates. A study by Kumar *et al.*[24] produced a high response rate in stages IIB–IVA with a combination of cisplatin, ifosfamide and bleomycin. Compared with radiotherapy alone, again there was no increase in overall or disease-free survival after 32 months of follow up. Similar results were obtained in a study by Souhami *et al.*[25] Responses after combination chemotherapy with bleomycin, vincristine, mitomycin and cisplatin were high, as well as the complete responses with the chemotherapy followed by radiotherapy. Surprisingly, the survival rates after 5 years were worse compared with a control group receiving radiotherapy alone. One problem in the design of the study was that the majority of patients were of very high risk (rate of lymph node metastasis: 63%; rate of positive para-aortic metastasis: 50%). The study has also been criticized because the numbers of evaluable patients in each arm were asymmetric. Further trials such as the ones from Cárdenas *et al.*[26] or Tattersall *et al.*[27,28] investigating neoadjuvant chemotherapy prior to irradiation were disappointing too, because they could not demonstrate any benefit in overall or disease-free survival. One reason for this effect could be a cross-resistance between radiotherapy and the different antineoplastic agents used in the trials. Another problem of standard-scheduled protocols with administration of chemotherapy every 3–4 weeks is the regrowth of tumor cells and acquisition of resistant subclones. It might also be hypothesized that chemotherapy resulted in a significant prevalence of anemia, finally leading to reduced tumor oxygenation, which is considered crucial to obtain optimal effect of radiotherapy.

Neoadjuvant chemotherapy prior to surgery

Compared with neoadjuvant chemotherapy prior to radiotherapy, the results of neoadjuvant chemotherapy prior to surgery are more promising. The reduction of tumor masses allows surgical treatment in primarily inoperable patients. Another advantage of this concept is the reduction of node-positive tumors. A possibly critical point of this strategy is the time to surgery. Therefore, monitoring by computed tomography or magnetic resonance imaging is essential. Sardi *et al.*[29] was the first to demonstrate the benefit of the sequence of neoadjuvant chemotherapy and surgery compared to radiation alone in large tumors. This trial was also the first which used a modern dose-dense schedule with administration of the cytotoxic regimen every 10 days. This procedure may allow us to

Table 7. Results of phase III trials comparing neoadjuvant chemotherapy (NACT) followed by radiation with radiation alone

Author	Patients (*N*)	Regimen for NACT	Local concurrent chemotherapy NACT+Rx versus Rx	Survival rates (%) NACT+Rx versus Rx
Chauvergne, 1988	172 (IIb–III)	2–4 VMCP	84 versus 87	62 versus 60 (2 years)
Cárdenas, 1991	28 (IIb)	4 × PEC	56 versus 62	–
Kumar, 1994	184 (IIb–IVa)	2 × BIP	–	38 versus 42 (32 month)
Souhami, 1991	107 (IIIb)	3 × BOMP	47 versus 32	23 versus 39 (5 years)
Tattersall, 1992	71 (IIb–IVa)	3 × PVB	65 versus 73	141 versus 167 weeks
Tattersall, 1995	260 (IIb–IVa)	3 × EP	43 versus 65	58 versus 70 (2 years)

suppress a regrowth of tumor cells more efficiently. Probably this is the reason why the authors were also able to demonstrate a benefit for the sequence of neoadjuvant chemotherapy prior to irradiation versus radiotherapy alone. However, contrary results to this study were published by Ting-Chang *et al.*,[30] who compared the efficacy of neoadjuvant chemotherapy followed by radical hysterectomy with that of radiotherapy for bulky early-stage cervical cancer. Neoadjuvant chemotherapy consisted of cisplatin and bleomycin, and was administered at 10-day intervals for three cycles. No benefit for survival rates was seen with neoadjuvant chemotherapy. This study needed 8 years to register 124 patients. The long duration of the study and the small number of patients included invalidates the conclusions to a certain extent. Encouraging response rates (i.e. 50–60%) have been reported when multiple-agent cisplatin-containing combination regimens were used in previously untreated cervical cancer patients.[31–34] Looking for new therapeutic strategies, taxanes have now been studied for the treatment of cervical cancer. Paclitaxel and docetaxel show a moderate response rate in cervical cancer when used as single agents.[35] The combination of platinum and taxanes could be more promising due to the non-overlapping or even synergistic cytotoxic activity of both substances, which may result in an additive antitumoral effect. This has been shown in other tumor entities including platinum-refractory ovarian[36] or small cell lung cancers.[37] We performed a phase I/II study with weekly administration of carboplatin and docetaxel for locally advanced primary (LACC) and recurrent cervical cancer. In 28 patients with LACC the response rate was 71.4% with five complete remissions.[38] Surgery could be performed successfully in all of the patients with partial and complete responses. In a neoadjuvant setting it is essential to administer the cytotoxic regimen not only at the highest tolerable dose, but also in a modern dose-dense schedule. Further studies including phase II trials in a neoadjuvant preoperative setting or randomized phase III trials comparing optimized chemotherapy and surgery with concurrent radio- and chemotherapy are necessary to define the role of neoadjuvant chemotherapy prior to surgery inclusively. This concept should thus be considered experimental and should not be used outside controlled clinical trials. A possible alternative therapeutic concept for the experienced pelvic surgeon could be primary surgery followed by postoperative chemoradiation as demonstrated by Boronow.[39] A 75% survival rate in 21 patients with bulky 6-cm barrel-shaped lesions was seen after primary surgery followed by simultaneous chemoradiation.

Radiochemotherapy

In the past two decades, many studies have established that treatment with cisplatin, fluorouracil and mitomycin can safely be combined with pelvic irradiation. The combination of both treatments may interact to increase the killing of tumor cells by inhibiting the repair of radiation-induced damage, initiating proliferation in non-proliferating cells and reducing the fraction of hypoxic cells that are resistant to radiation. Answers to the question whether there is any incremental benefit from the added chemotherapy have now come from five large randomized studies (Table 8). The first study by Thomas *et al.*[40] investigated the effect of a concurrent application of 5-FU in locally advanced cervical cancer. Survival rates (FIGO stage III: 50%; FIGO stage IV: 42%) were increased when compared to a historical control group.

Keys *et al.*[41] designed a study for the Gynecologic Oncology Group which comprised 369 patients with stage IB_2 cervical cancer. The study compared radiotherapy alone with a regimen of 6 weeks of cisplatin and pelvic irradiation. A significantly improved control of local disease and prolonged survival for concurrent use of cisplatin and radiation has been demonstrated. A study examining more advanced stages of the disease (stage IIB–IVA) was performed by Rose *et al.*[42] In total, 526 patients were randomized and received radiotherapy concomitantly with one of three chemotherapy regimens: weekly cisplatin, two courses of a three-drug combination consisting of hydroxyurea, cisplatin and fluorouracil or twice-weekly hydroxyurea. The important message of this study was the significantly higher progression-free survival rate at 24 months in the two groups that received cisplatin (67 and 64 versus 47%). Cisplatin alone showed a lower toxicity than the three-drug combination. The results of this study clearly demonstrated the benefit of concurrent single-agent chemotherapy with cisplatin. The concept of concurrent chemotherapy and radiotherapy was also supported by the results of the study by Morris *et al.*[43] who evaluated 386 patients with a wide range of stages of the disease ranging from bulky stage IB to stage IVA. The study compared the effect of radiotherapy to a pelvic and para-aortic field with that of pelvic radiation and three cycles of cisplatin and fluorouracil. The addition of chemotherapy improved cumulative rates of survival at 5 years significantly (73 versus 58%). Thomas[44] estimated the reduction in the risk of death in these trials of concurrent chemotherapy and radiotherapy. He found similar absolute improvements in survival and similar reductions of death from cervical cancer. The currently published trials suggest that

Table 8. Studies comparing the different setting of concurrent chemoradiotherapy with radiotherapy alone

Study	Patients (*N*)	FIGO stage	Progression-free survival (%)	Relative risk of death in comparison group
Keys *et al.*, 1999		IB_2		
RX alone versus RX+weekly	186		63	0.54
CDDP	183		79	
Rose *et al.*, 1999		IIB–IVA		
I: RX+hydroxyurea	177		47 (2 years)	I versus II: 0.61
II: RX+weekly CDDP	176		67	I versus III: 0.58
III: RX+CDDP/5-FU/hydroxyurea	173		64	
Morris *et al.*, 1999		IB_2–IVA		
RX alone versus	193		40 (5 years)	0.52
RX+CDDP/5-FU	195		67	
Peters *et al.*, 1999		IB, IIA		0.50
RX alone versus	116		63 (4 years)	
RX+CDDP/5-FU	127		80	

cisplatin-based chemotherapy should be given concurrently with radiotherapy. Weekly administration of cisplatin seems to be the most promising setting.

The new standard of concurrent cisplatin-based radiochemotherapy has been established after the publication of their data by Peters *et al.*[45] Chemotherapy and pelvic radiation was compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. In this study only the first two cycles of chemotherapy were administered concurrently. The third and fourth chemotherapy cycles were given when radiotherapy was completed. In total, 243 patients with clinical stage Ia_2–IIa were assessable. Patients in the radio/chemotherapy arm received bolus cisplatin 70 mg/m^2 and a 96-h infusion of fluorouracil 1000 mg/m^2/day every 3 weeks for four cycles. Only the first and second cycles were given concurrent to radiotherapy. The study showed a significantly improved progression-free and overall survival for patients with radiotherapy and chemotherapy. Interestingly, the subgroup analysis of those patients who only received one to two cycles of chemotherapy concurrent to radiotherapy showed survival rates not significantly different from the control group with radiotherapy only. Only those patients who received all four cycles of chemotherapy, including the two cycles administered after radiotherapy, demonstrated a benefit from therapy. This could be a hint that the effect of chemotherapy was not only a sensitization to chemotherapy but also or predominantly a systemic effect with elimination of distant micrometastasis. However, administration of sufficient doses of cytotoxic agents as part of radiochemotherapy seems to be essential. To ensure optimal conditions for radiochemotherapy, sufficient oxygenation of the tumor is crucial. Recently, a German randomized phase III trial[46] compared adjuvant sequential chemo-radiotherapy with and without erythropoetin in high-risk patients with carcinoma of the cervix. The study showed significantly lower rates of grade I–II anemia in patients receiving erythropoietin. To conclude all phase III studies investigating the role of concomitant radiochemotherapy, it should be emphasized that this therapy proved to be superior over radiotherapy alone in any therapeutic scenario investigated. Concurrent radiochemotherapy should thus be considered the standard of care in any situation in which previously radiotherapy was recommended.

Conclusions

During the last few years, systemic antineoplastic therapy has gained increased importance for the treatment of invasive cervical cancer. Although it is now accepted that untreated cervical cancer exhibits significant clinical chemosensitivity, recurrent or overt metastatic disease remains the most accepted indication for chemotherapy worldwide. For these patients, single-agent cisplatin at 50 mg/m^2 given every 3 weeks should be regarded as standard of care unless any combination regimen has demonstrated its superiority in terms of survival prolongation within a controlled randomized study. Combinations of platinum and ifosfamide or paclitaxel have led to both improved

response rates and progression-free survival, and may be considered a therapeutic alternative to single-agent platinum when rapid symptom control is required. Chemotherapy after failure from local irradiation remains a major clinical challenge, since efficacy of most agents in this situation is still unsatisfactory. A number of interesting new agents such as taxanes, camptothecin analogs, vinorelbine or gemcitabine have recently been introduced to clinical use, but their future role in the therapeutic repertoire still remains to be defined.

Although high response rates could be achieved in most studies performed so far, no data exists supporting the use of neoadjuvant chemotherapy prior to irradiation or surgical treatment apart from controlled clinical trials. However, neoadjuvant chemotherapy remains an attractive field of research due to its high activity, the improvement of local resectability and the considerable success achieved in other tumors such as breast cancer or tumors of the upper aerodigestive tract. Summarizing the recent preclinical and clinical developments, future neoadjuvant protocols for cervical cancer should incorporate agents which can be given at rapidly repeated intervals (e.g. platinum, taxanes, camptothecins, gemcitabine) and seek to prevent or normalize anemia which may severely impair the success of irradiation following chemotherapy.

Recently, the most significant progress has been made when chemotherapy is simultaneously given alongside with irradiation. Definitive chemoirradiation or adjuvant radiochemotherapy following radical surgery is now considered the standard of care instead of radiotherapy alone in patients presenting with high-risk primary disease. Weekly single-agent cisplatin at 40 mg/m^2 or platinum plus 5-FU are the current regimens of choice to be added to radiotherapy. This concept may be further improved by adding newer agents with defined radiosensitizing properties such as taxanes, camptothecins or gemcitabine. It should be emphasized, however, that cytostatics administered in addition to radiotherapy should be given at systemically relevant dosages in order to achieve optimal distant control, since systemic rather than local failure has been a major limitation of previous therapeutic concepts. Moreover, the role of adjuvant chemotherapy alone in high-risk operable cervical cancer needs further clarification. As a conclusion, chemotherapy is now accepted as an integral component of the treatment of invasive cervical cancer not only in palliative therapeutic situations but also in patients presenting with principally curable disease. Further investigations on chemotherapy of cervical cancer are warranted both to optimize its the use and to better understand its value in different therapeutic scenarios.

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