Induction Chemotherapy for Cervical Cancer

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20.1 Introduction

After breast cancer, cervical cancer is the second most common cause of cancer-related death, in women worldwide. In Western countries some 40,000 women die from advanced cervical cancer per year, in developing countries about six times as many. This dismal outcome in a highly preventable cancer can be improved by consistent early diagnosis in terms of Papanicolaou Screening. Early stage cervical cancer can be cured by surgery or radiotherapy alone. Advanced tumors, however, are at great risk of recurrence and account for the vast majority of deaths from cervical cancer. Therefore, the key to improve cure rates in cervical cancer consists of two components – first, enhancement of early diagnosis, which basically is manageable if resource settings are improved, and second, improvement of treatments in advanced cases with the goal to improve the therapeutic impact in terms of overall survival and quality of life. Another valuable endpoint might be therapy at reduced cost as compared to already existing treatments.

20.2 Therapy of Advanced Cervical Cancer

Therapy of advanced cervical cancer largely depends on the stage at the time of first diagnosis. Irradiation plays the major role in tumors restricted to the pelvic area. Concomitant chemotherapy with cisplatin reduces the relative risk of death by approximately 50% by decreasing local pelvic failure and distant metastases [1–5]. Stage I B2 lesions with tumors

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confined to the cervix can be treated with surgery alone, but the chances of adequate treatment are only 12% [6]. As a consequence primary stage I B2 tumors of more than 4 cm of diameter without invasion of the parametria are already considered advanced disease that requires postoperative adjuvant radiotherapy or radiochemotherapy. Thus there is an indication for radiochemotherapy in all stages from I B2 with tumors of more than 4 cm in diameter to stage IV A with invasion of the bladder or/and rectum. Even if pelvic exenteration might be taken into account for stage IV A disease, not invading the pelvic side wall without evidence of spread beyond the pelvis, the standard of care for downsizing is induction chemotherapy combined with external beam irradiation and intracavitary brachytherapy, in order to minimize the risk of relapse [7].

20.3 Brachytherapy

Intracavitary brachytherapy is the unique tool that makes it possible to apply effective doses of radiotherapy to affect advanced cervical cancer, much more than with external beam irradiation. Depending on stage and pattern of metastatic dissemination in locally advanced disease, it is combined with external beam irradiation. Nevertheless, radiotherapy alone fails to control progression in 35–90% [8].

In modern new dosimetric systems the radioactive sources are distributed in an applicator in defined doses to a designated treatment volume. Since brachytherapy is the only means to induce substantial and long-lasting remission due to extremely high local exposure to radiotherapy, every attempt should be made to deliver tumoricidal doses, even if the vulnerable adjacent tissues receive a slightly higher dose [9, 10]. Risk-adapted dosimetry, however, is not safe or precise enough to exclude collateral damage to adjacent tissues, and after a tumoricidal local dose has been administered, the risk of collateral damage cannot be excluded. Irrespective of its firm position in treatment programs, until recently with no better alternative, brachytherapy, in terms of toxicity should not be trivialized. As long as there is nothing less toxic, patients have to cope with the impact of radical radiation on bladder, rectal, psychosocial, and sexual function, with sometimes severe secondary effects like lymphedema of the legs, stenosis of the ureters, requiring stents or kidney fistulas, and last but not least, rectovaginal or vesicovaginal fistulas that reduce quality of life to a minimum [11, 12].

20.4 Intra-Arterial Infusion Chemotherapy

The goal of regional chemotherapy is to improve the efficacy of cytostatic drugs without causing additional discomfort to the patient [13]. In chemosensitive tumors like cervical cancer, regional chemotherapy can generate much higher local drug exposure at low toxicity, than systemic chemotherapy.

So far, there are only few studies addressing this concept. In a trial comprising 12 patients in clinical stages I to II b with tumors beyond 4 cm in diameter intra-arterial

infusion via the uterine artery in 7 out of 12 cases induced a tumor mass reduction of more than 50% of the initial volume after only two treatment cycles [14]. In another study, where intra-arterial infusion chemotherapy with cisplatin, adriamycin, and melphalan was administered via both internal iliac arteries, a remission induction of 65% was achieved, 8.3% (4/48 patients) of which were complete remissions and the remainder partial remissions. In two cases of complete remissions this was also confirmed histologically [15].

A trial of intra-arterial infusion of cisplatin via hypogastric arteries was performed in 25 patients with advanced (14/25 patients) or recurrent (11/25 patients) cervical cancer. 40 mg of cisplatin was infused over 60 min on each side. Eleven of the fourteen patients (78%) showed a good response and had radical hysterectomy, lymphadenectomy, and external beam radiation thereafter. In patients with recurrent disease, the overall response rate was 36%. Pain relief was obtained in all patients. After a mean follow-up of 23 months no pelvic recurrence had occurred [16].

Considering these data against the background of intensive radiotherapy, it seems obvious that achievement of optimal results without the threat of imminent toxicity is closely related to the optimal dosage and drug exposure in regional chemotherapy.

20.5 Isolated Pelvic Perfusion

Drug exposure can best be controlled with isolation perfusion techniques. Isolation of the pelvis is carried out via an arterial and venous femoral access. Both femoral vessels are cannulated with so-called stopflow-balloon catheters, which, after injection of chemotherapeutics into the arterial catheter, are blocked above the bifurcation of aorta and vena cava. Isolation of the pelvis is completed by means of upper thigh pneumatic cuffs (Fig. 20.1). After a 15 min isolation perfusion and deflation of the blocks, the drug levels in the systemic blood circulation are diminished by means of chemofiltration.

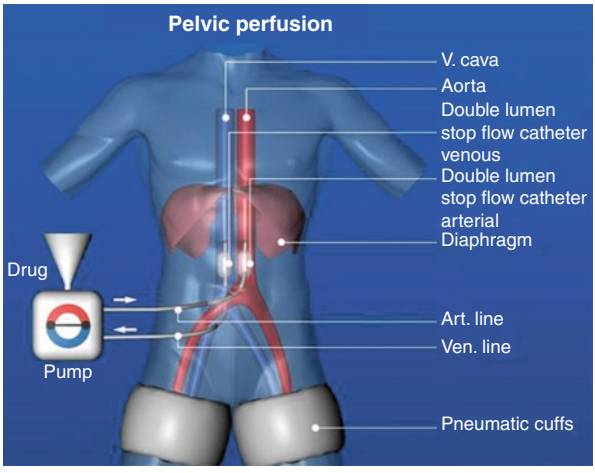

Fig. 20.1 Triple channel balloon catheters are introduced via the femoral vessels and the balloons blocked above the pelvic bifurcation of aorta and vena cava. The upper thighs are blocked with pneumatic cuffs. After a 15 minutes drug exposure, chemofiltration is started via the deblocked arterial and venous catheters

Consequently, by reducing systemic peak levels of drugs, systemic toxicity and side effects are alleviated. Local damage in pelvic organs does not occur and quality of life is usually undisturbed.

In a patient with advanced stage IV A disease with tumor invasion of the bladder, lymphnodes, and both parametria, a histologically complete remission after hysterectomy was revealed after four courses of isolated pelvic perfusion with cisplatin, adriamycin, and mitomycin. There was no significant systemic or local toxicity and the patient is in continuing complete remission after 6 years [17].

20.6 Discussion

The predominant role of radiotherapy in the treatment of advanced cervical cancer is derived from the unique tumoricidal effect of brachytherapy, which should be considered a "locoregional" therapy in terms of irradiation. So far, there are no studies of adequately effective treatment modalities, and therefore brachytherapy has a firm place in treatment protocols of cervical cancer. Locally enhanced radiotherapy, despite its effectiveness, bears a risk of severe local toxicity.

The question is whether achieving prolonged survival can justify extreme toxicity and unacceptable late side effects. As more and more acute and chronic treatment-related psychosocial and physical distress and dysfunction are identified, methods are desperately needed to reduce these adverse effects and toxicities [8]. If dose-intense radiotherapy could be completely or partially replaced by a less toxic but equally effective localized therapy, avoiding late irreversible side effects, patients would benefit greatly in terms of quality of life. This underscores the need for an equally potent but less toxic alternative.

Regional chemotherapy might be an option, but so far there is little experience in small studies [14–16] that do report promising results in terms of response rates and survival. Until now, intra-arterial chemotherapy has not been performed with uniform evidence-based protocols; however, regardless of which mode of application is chosen, results have been remarkable. It is noteworthy that intra-arterial infusion of pelvic arteries, as reported in the de Dycker study, may induce a complete remission induction of 23 months and more without causing any major toxicity. Another most important aspect in regional induction chemotherapy for cervical cancer is immediate tumor shrinkage after one to two cycles [14, 15]. Downsizing of locally advanced cancers to operability is observed in most cases, which makes intra-arterial induction chemotherapy appear to be comparable to brachytherapy, however, without collateral damage to adjacent tissues.

It therefore remains a challenge to determine the optimal mode of administering regional induction chemotherapy as intra-arterial infusion or isolated perfusion. The latter certainly requires experience in vascular infusion and perfusion techniques, but can be extremely effective and induce total tumor necrosis.

Therefore, a controlled study, clarifying whether regional chemotherapy can induce the same long-term results as external beam radiation and brachytherapy without causing local damage and intolerable toxicity, is more than overdue.

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