Long-lasting complete remission of a patient with cervical cancer FIGO IVB treated by concomitant chemobrachyradiotherapy with ifosfamide and cisplatin and consolidation chemotherapy – a case report

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Summary

The treatment of women with already metastasized cervical cancer at initial diagnosis represents a challenge to gynecologic oncologists. We report on a 63-year-old patient with locally advanced squamous cell carcinoma of the cervix uteri with an isolated metastasis to the left ovary. Following treatment with concomitant chemoradiotherapy with ifosfamide and cisplatin and three cycles of consolidation chemotherapy with the same drug combination a complete clinical remission could be documented. At present, 35 months after her disease was diagnosed, she is still without any evidence of disease. The very promising outcome of this patient might suggest that combined chemoradiation which is the standard treatment of locally advanced cervical cancer is justified as well in the metastatic setting, provided the metastatic lesion is covered within the usual radiation field.

Key words: Metastasized cervical cancer at initial diagnosis; Concomitant chemoradiation; Ifosfamide; Cisplatin; Consolidation chemotherapy.

Introduction

Cervical cancer is one of the most common cancers among women worldwide. Despite established screening programs with the aim of detecting cervical carcinoma in its early stages, many of them are only being diagnosed in locally advanced or even metastatic stages. Standard treatment for patients with locally advanced cervical carcinoma is concomitant cisplatin-based chemoradiotherapy [1]. In the case of metastatic disease the standard approach is to administer chemotherapy with only palliative intention. The combination of ifosfamide and cisplatin is one of the most active and affordable regimens throughout the world [2, 3]. Here we report the encouraging outcome of a patient with locally advanced cervical cancer with an isolated metastasis to the left ovary treated with curative intent, i.e. initial concurrent chemo(brachy)radiotherapy followed by consolidation chemotherapy.

Case Report

In August 2000, a 63-year-old female was referred to our institution due to advanced cervical cancer complicated by uremia. On admission her Eortem Cooperative Oncology Group (ECOG) status was 4; the serum levels of urea and creatinine were 19.4 mmol/l and 550 μmol/l, respectively. Gynecological examination revealed a large, exulcerative cervical cancer that easily bled during the examination. Moreover, a large mass in the area of the left ovary was discovered. Abdominal ultrasonography and computer tomography consistently showed a large, locally infiltrative primary tumor of the cervix uteri, a bilateral hydronephrosis (grade 3) and a tumor in the left ovary of 8.7 cm in diameter (Figure 1).

On admission, a bilateral nephrostomy was immediately performed, and excessive hydration was initiated. Thereafter, serum levels of urea and creatinine declined to normal levels. Nevertheless, the creatinine clearance remained at only 18 ml/min at the start of concomitant chemobrachyradiotherapy.

Histopathological examination of a punch biopsy of the cervical tumor revealed a grade 3 squamous cell carcinoma. The chest X-ray did not show any lung metastases. As the ultrasound and CT-findings could not differentiate between a simultaneous primary tumor of the left ovary or an isolated metastasis of squamous cell carcinoma of the cervix to the left ovary, an exploratory laparoscopy was performed. The biopsy of the ovarian tumor revealed a metastasis of the cervical squamous cell carcinoma. Accordingly the patient was classified as having a FIGO-Stage IVB cervical cancer.

The patient received two cycles of concomitant chemoradiotherapy with ifosfamide and cisplatin followed by three cycles of consolidation chemotherapy with the same drug combination. A standard radiation therapy was applied (external radiotherapy by the box technique without a central block plus brachyradiotherapy in a total dose of 80 Gy to point A). After five fractions of external irradiation, i.e., 10 Gy, low dose rate (LDR) brachyradiotherapy was delivered by one intracavitary insertion in a dose of 30 Gy to point A. A boost dose was given to the left ovary by a small, anterior-posterior field, 10 x 9 cm in size. The first chemotherapy cycle was given concurrently during LDR brachyradiotherapy consisting of cisplatin at a dose of 35 mg/m^2 (in 1-hour infusion) followed by ifosfamide at a dose of 2000 mg/m^2 (in 24 hours continuous infusion). During the last three days of external radiotherapy the patient received a second course of concomitant chemotherapy with cisplatin at the same dose (35 mg/m^2, day 1) and ifosfamide at a dose of 2000 mg/m^2/day on three consecutive days with uroprotection

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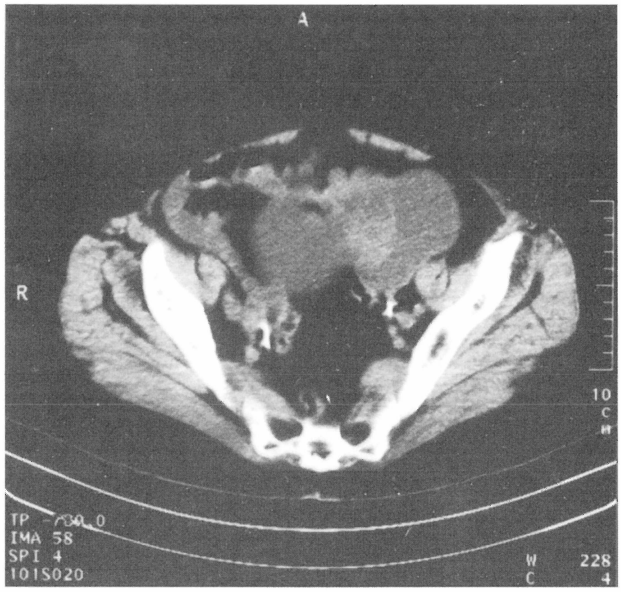

Figure 1. — CT finding on admission: isolated metastasis of a squamous cell carcinoma of the cervix uteri to the left ovary with a diameter of 8.5 cm.

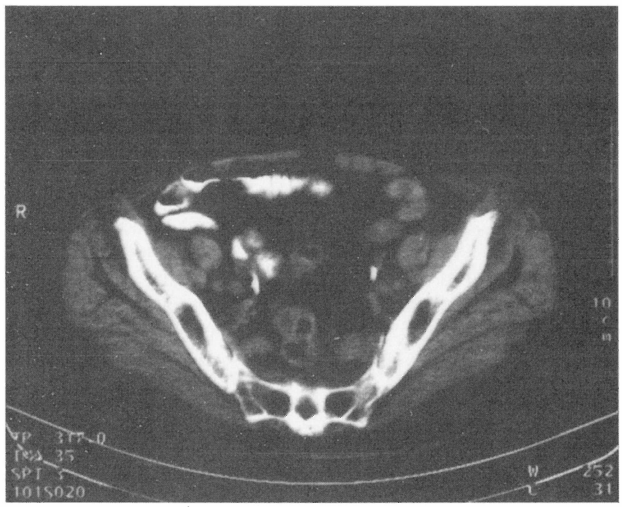

Figure 2. — CT finding after the end of treatment - there is no evidence of the previous metastasis to the left ovary.

by means of uromitexan at a dose of 60% of the ifosfamide dose, respectively. The first course of consolidation chemotherapy was administered 28 days after the second concomitant chemoradiotherapy cycle, and thereafter the courses were repeated every 21 days.

The treatment was well tolerated, and ECOG status improved during the treatment, from 4 at referral up to 1 at the end of the treatment. The major toxicities that were observed were grade 3 leukopenia and grade 2 anemia, respectively.

After completion of the treatment the gynecological examination with punch biopsy was repeated. Both examinations showed a complete clinical response without any evidence of disease. CT examination of the abdomen showed complete disappearance of the metastasis to the left ovary as well as of the primary tumor of the cervix uteri (Figure 2).

At present, 35 months after the initial diagnosis, the patient is without any evidence of either local or distant recurrence.

Discussion

Despite the advances in the management of locally advanced cervical carcinoma with surgery or concomitant chemoradiotherapy, the optimal management for disseminated, recurrent or persistent squamous cell carcinoma of the cervix has not been defined yet. Chemotherapy is the primary modality in the treatment of patients with disseminated disease at presentation with radiotherapy reserved for palliation of the symptoms. Many different chemotherapy agents have been evaluated regarding their activity in the treatment of cervical cancer. Among these, cisplatin is the most active single agent with response rates ranging between 20% and 30% [4]. Ifosfamide is the second most active agent with response rates of 22% [5]. The impact of any single agent in the treatment of metastatic cervical cancer has been minimal. This lack of efficacy of monochemotherapy led investigators to explore combinations of different chemotherapeutic drugs, especially the combination of cisplatin and ifosfamide (IC) [2, 3]. The response rates to IC-protocols ranged from 31% in the recurrent or metastatic setting [2] up to 80% in the neoadjuvant setting [3]. In the Gynecology Oncology Group (GOG) protocol 110, a three-arm, randomized phase III study, cisplatin alone was compared with the combination of cisplatin and ifosfamide and the combination of cisplatin and mitolactol [2]; in this trial the IC-combination yielded significantly higher response rates and a longer progression-free survival than either cisplatin alone or the combination of cisplatin and mitolactol. These findings led to the use of the IC-protocol as one of the standard regimens for the treatment of disseminated squamous cell cervical cancer.

Chemotherapy and radiotherapy can be delivered in three primary schedules: sequentially, alternating, and concomitantly. In contrast to the sequential and alternating approaches, in the concomitant schedule both treatment modalities, i.e. radiation therapy and chemotherapy, are applied simultaneously. This approach has the advantage of not delaying a potentially curative therapy, i.e. radiotherapy. In addition, this strategy minimizes the risk that cross-resistant tumor cells develop because there is no interval between the two modalities. However, the concomitant chemoradiotherapy schedule shows the most severe toxicity. Due to the mode of action of chemotherapeutical agents and because of the interaction of both, i.e. cytostatics and radiotherapy, the toxicity may be systemic and local. As already stated the most often used drug in the treatment of cervical cancer is cisplatin. Besides its direct activity against tumor cells, it could be shown that cisplatin can enhance the cytotoxic effects of radiation therapy against a variety of tumors, both in vitro and in vivo. Although the precise mechanisms as to how cisplatin increases the cytotoxicity of radiation has not been defined, the inhibition of repair mechanisms of radiation-induced sublethal damage and hypoxic cell sensitization have been postulated as possibilities.

A synergistic action between ifosfamide and radiotherapy was reported by Tonkin and co-workers [6]. They

showed the capability of ifosfamide to markedly enhance radiation cell killing. Ifosfamide did not show any radiosensitization effect when administered during fractionated radiation or high-dose rate brachyradiotherapy. In contrast, when ifosfamide was applied during low-dose rate brachyradiotherapy (5 cGy/min) it enhanced radiation cell killing to a large extent.

Recently, the results from five randomized phase III trials have shown an overall survival advantage for cisplatin-based chemotherapy given concurrently with radiotherapy. Although these trials varied somewhat in terms of stage of disease, dose of radiation, and schedule of radiation and cisplatin, they all demonstrated a significant survival benefit of 30% to 50% when cisplatin-based chemotherapy was administered concurrently with radiation therapy. Based on these results the National Cancer Institute proposed cisplatin-based concurrent chemoradiotherapy as standard therapy in the treatment of women with advanced cervical cancer [1]. The results of a meta-analysis show that, in addition to the improved control of local disease, chemotherapy applied during radiotherapy also has a statistically significant impact on the incidence of distant metastases [1].

The positive impact of adjuvant chemotherapy following concomitant chemoradiation was shown by Peters et al. in a subgroup analysis of the concomitant chemoradiation arm of their prospective, randomized study: patients who received one or two adjuvant cycles of cisplatin and 5-fluorouracil chemotherapy in addition to the two concomitant chemoradiation cycles had a significantly better survival than those who received only one or two cycles administered concomitantly to external radiotherapy [8].

Based on the well established activity of the combination of ifosfamide and cisplatin in the treatment of recurrent and/or metastasized cervical carcinoma as well as on their established radiosensitizing effects and the beneficial effects of concomitant chemoradiotherapy in the treatment of locally advanced cervical cancer, we tested concomitant chemobrachyradiotherapy with ifosfamide and cisplatin in locally advanced squamous cell carcinoma of the uterine cervix FIGO-Stages IB2 (bulky) – IVA [9]. In a total number of 44 patients a 100% complete clinical response rate, also evidenced by cervical punch biopsies, was obtained three months after completion of the concomitant chemobrachyradiotherapy treatment; after a median follow-up of 20 months the recurrence-free and overall survival were 93% and 95%, respectively. Based on these highly promising results we initiated the same treatment of initial concomitant chemo(brachy)radiotherapy followed by consolidation chemotherapy for our patient with FIGO Stage IVB cervical carcinoma with the primary intention of cure. The complete response and the disease-free status of the patient 35 months after her advanced and metastasized cancer was diagnosed justify this approach.

In conclusion, we believe that even patients with disseminated primary cervical cancer at diagnosis, provided the metastatic lesion is covered within the usual radiation field, should be treated as aggressively as possible, combining both modalities, i.e. radiotherapy and chemotherapy, taking into account the patients' general performance status, expected survival time, tumor burden, and status of kidney, liver and bone marrow function.

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