

Review

## Postoperative Therapy Modalities for Cervical Carcinoma

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**Abstract.** *Currently, the standard therapy for cervical carcinoma of FIGO stage IIB following adequate radical surgery is simultaneous radiochemotherapy with a platinum chemotherapeutic agent. According to the current state of scientific knowledge, all patients of FIGO stages IIA–IB with at least one additional risk factor (adenocarcinoma, pN1, L1, V1, pT1b2) also benefit from adjuvant radiochemotherapy. Various studies have shown that it is possible to successfully carry out a platinum radiochemotherapy. However, one disadvantage is that a number of patients have to break off therapy because of treatment-related toxicities. It has also been proven that a low hemoglobin level during radiochemotherapy is a negative prognostic factor for overall survival. The data regarding a possible survival advantage following an increase in the hemoglobin content in the blood of cancer patients by erythropoietin administration is still contradictory. As a result, the administration of new cytostatics, platinum combination chemotherapies, sequential instead of simultaneous regimens and appropriate supportive therapies have to be taken into account. Several studies are currently being conducted into the effectiveness of such new therapies on both life expectancy and quality of life (e.g., Cervix-NOGGO-AGO-Uterus 7-study).*

Worldwide, invasive cervical carcinoma is the second most frequent form of malignant disease in women (1). There is a clear discrepancy in the incidence and mortality rates between highly developed and less developed countries. In the highly developed industrial states, the rate of cervical carcinoma among all cancer cases in women is 3.6%, with a mortality rate among women with cancer of 3.3%, ranking it

as the seventh most malignant disease of women. In contrast, in less developed countries the incidence of cervical cancer is 15%, placing it second in terms of frequency of cancer, while with respect to mortality it is the leading cause of death (13.5%) (2).

In Germany, the incidence rate has been falling, currently being 12-15 new cases per 100,000 population per year, as has the rate of lethality, currently at 6/100,000 per year. This trend, over approximately the last 20 years, of decreasing disease rates is due to the introduction of routine screening. The distribution and emergence pattern of cervical carcinoma has all the characteristics of a sexually-transmitted disease.

Infection with human papilloma viruses, HPV 16, 18, as well as 31, 33, 45, are the most frequently detected sub-types in cervical cancer, although over 100 different genotypes have been identified. In a recently published epidemiological study, however, sub-types 35, 39, 51, 52, 56, 58, 59, 68, 73 and 82 were classified as oncogenic or as belonging to the high-risk group. The sub-classes 26, 53 and 66 are currently classified as possible oncogenes (3). Of great significance for carcinogenesis are the so-called co-factors such as local infections (e.g., chlamydia, HSV-2), nicotine abuse, acquired immune deficiency (e.g., AIDS), as well as genetic changes. In recent years, there has been a continuous reduction in the average age of patients at the time of first diagnosis (4). Approximately 80-85% of the cervical cancers are squamous cell carcinomas, while the proportion of adenocarcinomas is 15-20%. The stage of the disease is determined using FIGO guidelines, which are based on the histological findings of the primary tumor, clinical examination and palpation. The FIGO stage classification provides the basis for therapy (5).

Although notable progress has been made both in the treatment of cervical cancer and efforts to obtain early diagnoses, a considerable number of patients suffering from early stage cervical cancer experience a relapse, despite radical surgery or radiotherapy as a primary treatment (6).

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### Standard adjuvant therapy

Currently, the standard therapy for a cervical carcinoma of stage FIGO IIB after adequate radical surgery, is simultaneous radiochemotherapy with a platinum chemotherapeutic agent. Current knowledge indicates that all patients of stages FIGO IIA-IB with at least one additional risk factor (adenocarcinoma, pN1, L1, V1, pT1b2) also profit from adjuvant radiochemotherapy. Peters *et al.* showed that simultaneous radiochemotherapy with cisplatin significantly improved progression-free survival and overall survival in surgical patients (Piver 3) of stages IB-IIA as compared to radiotherapy alone (7). This study was conducted on 243 patients with risk factors, and led to the conclusion that, for carcinomas in an early stage, a combination of surgery followed by chemotherapy and radiation leads to a significant improvement in prognosis, especially if the tumor size is more than 2 cm or  $\geq 2$  lymph nodes are involved (8). These data from Peters *et al.* agree with data that had been previously obtained by Whitney *et al.*, Keys *et al.*, Morris *et al.* and Rose *et al.* in randomized comparisons of radiotherapy and various platinum chemotherapies (9-12). Whitney *et al.* showed, in 386 inoperable patients, that treatment with cisplatin ( $50 \text{ mg/m}^2$ ) and 5-FU ( $1000 \text{ mg/m}^2$ ) in combination with simultaneous radiation led to a significantly increased overall survival ( $p=0.018$ ) compared to hydroxyurea ( $80 \text{ mg/m}^2$ ) in combination with radiotherapy (9). The GOG#120 study (Gynecologic Oncology Group) of Rose *et al.* also showed, in 536 inoperable patients with cervical cancer, that cisplatin monotherapy ( $40 \text{ mg/m}^2$ ) was as effective as a cisplatin ( $50 \text{ mg/m}^2$ ), 5-FU ( $1000 \text{ mg/m}^2$ ) and hydroxyurea ( $2 \text{ mg/m}^2$ ) combination therapy (12). As very recently published, even for a protracted venous infusion of 5-FU in advanced cervical cancer ( $225 \text{ mg/m}^2/\text{d}$  for 5 d/week for 6 cycles during radiotherapy), no advantage in outcome over weekly cisplatin with pelvic radiation was detectable (GOG#165) (13). Keys *et al.* obtained a significant increase in survival rate using combined radiochemotherapy ( $40 \text{ mg/m}^2$ ) as compared with primary radiotherapy alone, in 368 operable patients with stage FIGO-IB1 carcinoma (10).

In conclusion, it can be said that the data gathered to date demonstrate that combined radiochemotherapy is superior to radiation treatment alone. These results were confirmed in a meta-analysis carried out by Green *et al.* (14), showing the absolute survival benefit of a platinum radiochemotherapy to be 10%. Combination chemotherapy with cisplatin was equivalent to cisplatin monotherapy. This is the foundation for the current standard therapy of  $40 \text{ mg/m}^2/\text{week}$  of cisplatin with simultaneous radiation therapy for 6 weeks. In their meta-analysis, Green *et al.* also showed that in studies in which at least 70% of the patients were FIGO stage I or II, the positive effect of

chemoradiotherapy was greater than in studies with fewer than 70% FIGO stage I and II patients ( $p<0.006$ ). However, the interpretation of the data was rendered difficult by heterogeneity in the studies with higher tumor stages (14).

### The role of the hemoglobin level in the treatment of cervical cancer

Patients with a cervical carcinoma often develop anemia as a result of the tumor and/or the treatment. Prior to the start of adjuvant therapy it is necessary to determine the hemoglobin level, otherwise the effectiveness of the radiation therapy may be affected.

Anemia due to the tumor can result from the malignant disease process, as an effect of bleeding, nutritional deficits or damage, as well as tumor infiltration of the bone marrow or an immunological influence on erythropoiesis. However, it is usually iatrogenic, as the result of a myelosuppressive chemotherapy and/or radiotherapy (15). Groopman and Itri, in an overview of the published clinical studies, found that the incidence of grade 1/2 and grade 3/4 anemias after chemotherapy for solid tumors can be as much as 100% and 60%, respectively (16). In the adjuvant chemotherapeutic treatment of cervical carcinoma carried out by Peters *et al.* and Blohmer *et al.*, up to 60% of the patients developed grade 1/2 anemia and up to 10% grade 3/4 anemia (7,17). In addition, anemia affects many aspects of the quality of life, leading to functional deficits that influence the subject's sense of well-being (18).

One of the most frequent clinical symptoms of anemia is fatigue. Although fatigue can be multifunctional, anemia is an important, treatable cause of it (19). There is an objective correlation between the hemoglobin (Hb) levels and the quality of life in cancer patients (16, 20). Cella (20) showed that patients with an Hb level  $>12 \text{ g/dl}$  suffered significantly less from fatigue, had fewer other symptoms of anemia and had a better quality of life than patients with Hb levels  $<12 \text{ g/dl}$ . In addition, a meta-analysis demonstrated that a low Hb level is a negative prognostic factor for survival (21). In a retrospective study, Grogan *et al.* found that, in cervical cancer patients who had received radiotherapy, there were clear differences in survival depending on the Hb level obtained during radiotherapy (22). The 5-year survival rate for patients with Hb  $>12 \text{ g/dl}$  was 74%, whereas for Hb  $<11 \text{ g/dl}$  it was only 45%. Two very recent studies found the Hb level before adjuvant radiotherapy to be highly predictive of outcome in patients with cervical carcinoma (23, 24).

These results are in agreement with those of 3 prospective randomized studies in which the effect of administering erythropoietin-stimulating factors on survival parameters was investigated (17, 25, 26). In contrast to this, no survival advantage was observed in 2 prospective

randomized studies of patients who received myelo-supportive epoetin (27, 28). In a placebo-controlled multicenter study of 939 randomized breast cancer patients with metastases, who had received epoetin alpha in addition to the first-line chemotherapy, the overall survival rate after 12 months was significantly worse in the epoetin alpha group ( $p < 0.0117$ ), with the increased rate of mortality occurring during the first 4 months of treatment. This unexpected result was partly explained by the fact that patients who had been randomized into this arm of the therapy had increased risk factors for thromboembolic events, were older, in a poorer general condition, as well as in an advanced stage of the disease, as compared to the patients that were in the placebo arm (27). In the second multicenter study of 351 patients with head and neck cancers, which was also prospectively randomized and placebo-controlled, the patients administered epoetin therapy surprisingly showed a significantly reduced progression-free interval ( $p < 0.0008$ ). It must be noted critically that only 61% of the patients were treated in conformity with the therapy protocol, not allowing for significant evaluation.

According to current scientific knowledge, the selected target Hb levels (14.0 g/dl for women and 15.0 g/dl for men) are too high (28). A transfer of these results to other types of tumors, for example to cervical tumors, would not seem to be meaningful at this time. According to the study of Blohmer *et al.*, which was the first completed phase III trial to deal with the question of the significance of the hemoglobin concentration on the length of the relapse-free period and overall survival for adjuvant treatment of cervical carcinoma. A trend for a longer progression-free period can be detected following epoetin therapy. This was a randomized study of combined adjuvant sequential radiochemotherapy of cervical cancer with carboplatin and ifosfamide, with simultaneous administration of erythropoietin as compared to no administration of erythropoietin. In a group of 256 patients, it was shown that the additional administration of erythropoietin significantly reduced the rate of anemia ( $p = 0.001$ ). It was possible to keep the Hb level constantly above 12 g/dl both during chemotherapy and radiotherapy by erythropoietin administration, in contrast with a control group in which erythropoiesis was not stimulated (42% vs. 12%,  $p = 0.0001$ ). The mid-grade to high-grade anemias were reduced significantly. Further, the frequency of transfusion during chemotherapy was also reduced significantly (10% vs. 32%;  $p = 0.0002$ ). Moreover, the current interim analysis showed an increase in the frequency of freedom from relapse in the erythropoietin group (81% vs. 70% after a median of 2 years following treatment,  $p = 0.058$ ) (17).

An explanation for the connection between the Hb level and survival is tumor hypoxia. Tumor hypoxia is a

therapeutic problem since it makes solid tumors unresponsive to ionizing radiation and certain cytostatics (29). It has been shown, in animal experiments, that cytostatics (in particular alkylating agents) stem the growth of tumors significantly more at higher Hb levels (30-32). Equally complex are the relationships between anemia, tumor hypoxia, treatment resistance, tumor growth and malignant progression, described by Blohmer *et al.* (33). In the light of current knowledge, anemia can be an independent predictor of outcome in patients treated with chemotherapy and radiotherapy. In comparison to other prognostic factors in cancer patients, the Hb level can be corrected by administration of recombinant human erythropoietin (epoetin alfa). To elevate hemoglobin levels may, therefore, not only improve the effectiveness of standard cancer therapies, but also lessen fatigue and improve quality of life (33).

### New therapies

Evaluation of the standard therapy by researchers showed that, in general, it was possible to carry out simultaneous radiochemotherapy in conformity with the protocol. However, long-term results with regard to possible late toxicity effects are still lacking (34). As a criticism, it must be noted that a high percent of the patients did not receive the intended number of cisplatin cycles. An analysis by Sierkies *et al.* showed that only 45% of the patients had been able to receive the planned full dose of cisplatin in simultaneous radiochemotherapy (35). In the GOG-120 study, only 49% of the patients had received 6 cycles of the planned weekly cisplatin therapy (12). Thus, it must be considered whether the administration of new cytostatics and of a sequential instead of a simultaneous regime might result in a larger proportion of patients being able to undergo the planned number of cycles. On introducing such new therapies, it has to be evaluated whether the combination of newer cytostatics with the reduced effect of radiosensitivity, which results from sequential administration of radiotherapy, might not have a negative effect on the overall survival of the patients, despite an improvement in their quality of life.

Several studies are currently being conducted regarding the effectiveness of other cytostatics on overall survival. The combination of paclitaxel with a platinumous chemotherapeutic agent has attracted considerable interest. That the combination of a platinum derivative with paclitaxel might be beneficial has been suggested by *in vitro* data, which showed the synergistic effect of the 2 substances (36). There are several reports of a good response rate in cases with advanced cervical cancer or a relapse. Kudelka *et al.* showed that, in 32 untreated patients with advanced cervical cancer or a relapse, there was a 25% response rate on treatment with paclitaxel (37).

Recently, the results of the randomized study of the GOG (Protocol 169) on the first-line treatment of advanced cervical carcinoma (FIGO IVB, persistent disease or relapse) with cisplatin vs. cisplatin/paclitaxel were published. Of the 264 patients that had been evaluated (164 of whom had previously received radiotherapy), Moore *et al.* were able to show that the combination of cisplatin plus paclitaxel (50 or 135 mg/m<sup>2</sup>, q3w; up to 6 cycles) was clearly superior to cisplatin monotherapy (50 mg/m<sup>2</sup>) with regard to the response rate (cisplatin/paclitaxel 36% vs. cisplatin 19%;  $p=0.002$ ) and the median progression-free period (cisplatin/paclitaxel 4.8 months vs. cisplatin 2.8 months  $p<0.001$ ). Nonetheless, no significant advantage for overall survival was observed with the combination therapy (cisplatin/paclitaxel 9.7 months vs. cisplatin 8.8 months) (38).

The side-effects were an increase in grade 3/4 neutropenia and anemia. However, the quality of life in both arms of the investigation was the same, despite the increased myelosuppression in the combination arm (39). In 2001, Mickiewicz *et al.* examined the combination carboplatin plus paclitaxel as first-line treatment for advanced cervical carcinoma (carboplatin AUC5; paclitaxel 175 mg/m<sup>2</sup>, q3w; up to 6 cycles). Of 32 patients who had never received chemotherapy, 7 experienced a complete remission with this combination therapy and 16 had partial remissions, for a total response rate of 72%. The median progression-free interval was 7 months. The side-effects were tolerable (40). These results were confirmed, in small patient collectives with a low median follow-up, at the ASCO meetings of 2003-2005 (25, 41-43).

*In vitro* data indicated that gemcitabine at small doses is a potent radiosensitizer (44). The administration of weekly gemcitabine at 300 mg/m<sup>2</sup> combined with radiotherapy in patients with advanced cervical cancer (n=19 patients) resulted in a complete response rate of 89% (45). In metastatic cervical cancer patients, a high response rate was induced by the polychemotherapy of gemcitabine and cisplatin (n=40 patients), with complete response 7.5% and partial response 67.5% (46). Three phase II studies from Latin America combined 125 mg/m<sup>2</sup> gemcitabine with weekly cisplatin and standard pelvic radiotherapy in the treatment of cervical cancer (47-49). In these trials, with gemcitabine given after cisplatin, a high treatment response with acceptable overall toxicity were reported. The recent phase I trial of the Puget Sound Oncology Consortium used, instead, the reverse drug sequence of gemcitabine before cisplatin (50). Adding low-dose gemcitabine (50-100 mg/m<sup>2</sup>) to cisplatin and radiotherapy resulted in an excellent response, but the toxicities, especially clinically significant ototoxicity in the form of tinnitus, were unacceptable. Ototoxicity is known to be a side-effect of cisplatin. Therefore, the researchers hypothesized that the tinnitus resulted from a cisplatin sensitization effect by gemcitabine

(50). At the ASCO 2005, 3 further studies were presented with results of gemcitabine combined with a concurrent radio- and/or chemotherapy regimen in locally advanced cervical carcinoma. De Dios *et al.* could not obtain a statistical difference in terms of overall response rate (ORR) between combined low-dose gemcitabine plus cisplatin (n=53, 5x gemcitabine: 2x20 mg/m<sup>2</sup> and cisplatin: 30 mg/m<sup>2</sup>, weekly) and cisplatin monotherapy (n=49, 5x cisplatin: 30 mg/m<sup>2</sup>, weekly) (ORR: 89% vs. 98%, respectively) (51). Mas *et al.* concluded that the treatment with these 2 agents, gemcitabine and cisplatin, is both active and safe. Combining 125 mg/m<sup>2</sup> gemcitabine with 40 mg/m<sup>2</sup> cisplatin weekly for 5 weeks resulted in a pathological complete response of 81.8% (n=22) (52). Likewise, Boualga *et al.* described the concurrent monotherapy with gemcitabine (300/500/600 mg/m<sup>2</sup>, d1,8,40,47) as highly active with acceptable toxicity (complete response 74%, n=19 patients) (53).

Moreover, it has been previously shown that cisplatin in combination with the semi-synthetic vinca alkaloid vinorelbine has a beneficial effect on outcome in patients with carcinoma of the uterine cervix (54, 55). Therefore, the GOG conducted a trial to evaluate the efficacy and toxicity of this regimen in 73 patients with advanced and recurrent squamous cell carcinoma. The results were described as moderate (response rate 30%, neutropenia grade 4 67%), but further investigation within this patient population seems to be justified (56).

The topoisomerase-I-inhibitors irinotecan and topotecan have also attracted attention because of their reported antitumor activity against cervical cancer, as well as the ability to potentiate cisplatin's activity (57-60). In a recently published study, weekly cisplatin and irinotecan showed disappointing results in first-line treatment of patients with advanced, persistent or recurrent squamous cell carcinoma of the cervix. Thus, the GOG does not plan to undertake a phase III trial at the present time (61). In contrast, a further study of the GOG (Protocol 179) carried out with 293 patients with advanced squamous cell cancer of the cervix uteri, or a relapse, showed a significant survival advantage for the polychemotherapy regime with topotecan (cisplatin 50 mg/m<sup>2</sup>, d1,q3w. – 6.5 months *versus* cisplatin 50 mg/m<sup>2</sup>, d1/ topotecan 0.75 mg/m<sup>2</sup> d1-3, q3w. – 9.4 months;  $p<0.015$ ). Hematological toxicity was more frequent and more severe in patients receiving the combination chemotherapy. Grades 3 and 4 neutropenia were observed in 70% of the patients in the cisplatin plus topotecan arm compared with 1.4% in patients treated with cisplatin alone (62). Surprisingly, the more toxic combination regimen produced no significant reduction in quality of life (63).

The promising data with respect to the taxanes has led the German AGO (Arbeitsgemeinschaft für Gynäkologische Onkologie – Study Group for Gynecological Oncology) and the NOGGO (Nordostdeutsche Gesellschaft für

Gynäkologische Onkologie – North German Society for Gynecological Oncology) to begin a further study. Its goal is to compare the effectiveness and the tolerability of adjuvant chemotherapy with sequential radiotherapy as opposed to simultaneous radiotherapy in patients with cervical carcinoma of stages FIGO IB–IIB. The study is a multicenter, randomized phase III investigation into which 300 patients will be accepted over the course of 36 months. The central question is which modality – simultaneous or sequential radiochemotherapy – in the adjuvant treatment of cervical carcinoma brings advantages for progression-free and overall survival. In this phase III study, the effectiveness and tolerability of paclitaxel and carboplatin in sequential administration with radiotherapy will be compared with simultaneous radiochemotherapy with cisplatin. After the usual Wertheim-Meigs surgery, the patients in stages FIGO IB–IIB will be randomized into the 2 arms of the therapy: in arm A the patients will be treated sequentially, starting with 4 cycles of chemotherapy with paclitaxel and carboplatin, followed by 6 weeks of radiotherapy with a total dose of 50.4 Gy; in arm B, the patient regime will be simultaneous radiochemotherapy with weekly cisplatin and an equivalent total radiation dose of 50.4 Gy. On the basis of the Cervix-I-NOGGO-AGO study, all patients will receive darbepoetin alpha over the full course of treatment (17). The current standard treatment will be compared with a combination chemotherapy in the experimental arm of the study.

## Conclusion

In general, it can be concluded that the studies carried out so far and the attempts to combine different methods of treatment have resulted in considerable progress in the adjuvant treatment of cervical carcinoma. Nonetheless, new therapy procedures still have to be sought to enhance the quality of life of patients with high-risk cervical cancer and to increase their life expectancy.

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