A randomized phase III adjuvant study in high-risk cervical cancer: simultaneous radiochemotherapy with cisplatin (S-RC) versus systemic paclitaxel and carboplatin followed by percutaneous radiation (PC-R): a NOGGO-AGO Intergroup Study


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Background: Simultaneous adjuvant platinum-based radiochemotherapy in high-risk cervical cancer (CC) is an established treatment strategy. Sequential paclitaxel (Taxol) and platinum followed by radiotherapy may offer further advantages regarding toxicity.

Patients and methods: An open-labeled randomized phase III trial was conducted to compare paclitaxel (175 mg/m2) plus carboplatin (AUC5) followed by radiation (50.4 Gy) (experimental arm-A) versus simultaneous radiochemotherapy with cisplatin (40 mg/m2/week) (arm-B) in patients with stage IB–IIB CC after surgery. Primary objective was progression-free survival (PFS).

Results: Overall, 271 patients were randomized and 263 were eligible for evaluation; 132 in arm-A and 131 in arm-B appropriately balanced. The estimated 2-year PFS was 81.8% [95% confidence interval (CI) 74.4–89.1] in arm-B versus 87.2% (95% CI 81.2–93.3) in arm-A (P = 0.235) and the corresponding 5-year survival rates were 85.8% in arm-A and 78.9% in arm-B (P = 0.25). Hematological grade 3/4 toxicity was higher in arm-B. Alopecia (87.9% versus 4.1%; P < 0.001) and neurotoxicity (65.9% versus 15.6%; P < 0.001) were significantly higher in arm-A. Early treatment termination was significantly more frequent in arm-B than in arm-A (32.1% versus 12.9%; P = 0.001).

Conclusions: Sequential chemotherapy and radiation in high-risk CC could not show any significant survival benefit; however, a different toxicity profile appeared. This sequential regime may constitute an alternative option when contraindications for immediate postoperative radiation are present.

Key words: cervical cancer, morbidity, percutaneous radiation, radiochemotherapy, sequential treatment, survival

Introduction

Cervical cancer (CC) constitutes the leading cause of cancer death among women in low-income countries [1, 2]. In early, locally restricted CGs, surgery remains a major step of the therapeutic management. In women, however, who are considered to be at high risk for recurrence due to additional risk factors, such as positive resection margins, positive lymph node status, microscopic parametrical involvement or a bulky tumor >4 cm, an adjuvant therapy following radical hysterectomy has been recommended [3–5].
The value of combination chemotherapy with platinum agents has been demonstrated for recurrent, metastasized and advanced CC. The combination of paclitaxel and carboplatin has been shown to offer further advantages in regard to toxicity over the course of sufficient tumor control in numerous trials, thus rendering a promising and well-tolerated combination regime in advanced and recurrent CC [6–10].

We present here the results of the first randomized trial to compare efficacy and toxicity of adjuvant simultaneous radiochemotherapy with cisplatin versus sequential paclitaxel plus carboplatin and radiation in patients with high-risk CC after radical hysterectomy and lymphadenectomy.

patients and methods

patients

Patients were eligible for this phase III study if they fulfilled the following criteria: age ≥18 years, histologically confirmed CC (adenocarcinoma, squamous/adenosquamous carcinoma) after radical hysterectomy; International Federation of Gynecology and Obstetrics (FIGO)-stage IB2–IIB or IB1 when at least one of the following risk factors was present: lymphangioinvasion or haemangioinvasion (L1, V1), positive lymph node status (N1) or positive microscopic tumor margins (R1)—as opposed to clear macroscopic tumor margins (R0). According to current literature, 2-year progression-free survival (PFS) for this population is ~75%. Patients were excluded from the study if they had distant metastases; FIGO-stage ≥III; positive paraaortic lymph nodes; neuroendocrine carcinomas; prior systemic, hormonal or radiation therapy; advanced cardiac or renal insufficiency, peripheral neuropathy and active infection. Institutional review and ethics boards approved the study. The study was certified from the North-Eastern German Society of Gynecological Oncology. An independent monitoring institute was responsible for data control, quality checks and monitoring.

All patients provided a signed informed consent in accordance with institutional and federal guidelines. Patients’ characteristics are presented in Table 1.

study design and treatment

The investigation was conducted at 43 German institutions by a central randomization. Patients were randomly assigned to receive one of the following radiochemotherapy schedules: (i) four cycles of paclitaxel (175 mg/m²) (Taxol®, Bristol-Myers Squibb, Munich, Germany) plus carboplatin (Carboplat®, Bristol-Myers Squibb) were administered three-weekly. Premedication included i.v. 20 mg dexamethasone, 2 mg clemastine and 300 mg cimetidine.

arm-B

Cisplatin (Platinex®, Bristol-Myers Squibb) was administered i.v. at a dose of 40 mg/m² over 40 min in a weekly regime. Radiation was applied simultaneously in fractions of 1.8 Gy daily, five times a week up to a total of 50.4 Gy.

In both arms, patients with hemoglobin values of ≥10.5 g/dl received darbepoetin α 2.25 μg/kg/week on day 1 of the chemotherapy and repeated every 21 days. Patients with hemoglobin values of <10.5 g/dl received darbepoetin α 4.5 μg/kg/week on day 1 of each chemotherapy cycle up to a hemoglobin value of 13 g/dl.

Dose adjustments or interruptions of either drug were undertaken based on toxicity using standard criteria for both drugs. The chemotherapy dose was reduced by 25% for any grade 3 or 4 toxicity according to the National Cancer Institute—Common Toxicity Criteria [11] (NCI-CTC) version 3.0.22.
Table 2. Treatment-related data and concomitant medication

<table>
<thead>
<tr>
<th></th>
<th>Arm-A sequential</th>
<th>Arm-B simultaneous</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose overall (Gy)</td>
<td>45.6 (15.3)</td>
<td>45.8 (13.2)</td>
<td>0.883</td>
</tr>
<tr>
<td>After loading</td>
<td>26 (19.7)</td>
<td>26 (20)</td>
<td>1.0</td>
</tr>
<tr>
<td>Dose overall (Gy) including after loading</td>
<td>47.7 (16.5)</td>
<td>48.0 (14.6)</td>
<td>0.851</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zero</td>
<td>6 (4.5)</td>
<td>7 (5.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incomplete (1–3 cycles, respectively, 1–5 cycles)</td>
<td>6 (4.5)</td>
<td>39 (30)</td>
<td></td>
</tr>
<tr>
<td>Complete (4 cycles, respectively, 6–7 cycles)</td>
<td>120 (91)</td>
<td>85 (65)</td>
<td></td>
</tr>
<tr>
<td>Interruption of infusion</td>
<td>16 (12.6)</td>
<td>9 (7)</td>
<td>0.206</td>
</tr>
<tr>
<td>Dose modification</td>
<td>0 (0)</td>
<td>5 (4)</td>
<td>0.029</td>
</tr>
<tr>
<td>Cycle shift</td>
<td>24 (19)</td>
<td>37 (30)</td>
<td>0.055</td>
</tr>
<tr>
<td>Concomitant medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Darbepoetin</td>
<td>105 (87.5)</td>
<td>78 (69.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>G-CSF</td>
<td>6 (5)</td>
<td>18 (15)</td>
<td>0.010</td>
</tr>
</tbody>
</table>

G-CSF, granulocyte colony-stimulating factor. Values in bold are statistically significant.

Anticoagulation was not mandatory but reserved only for cases with thrombosis or thrombophilia.

radiation

Simultaneous radiochemotherapy began at the earliest 3–4 weeks after surgery, while sequential radiation started 2–3 weeks after completion of the last chemotherapy cycle. In cases of delayed or impaired wound healing, longer intervals up to radiation were possible according to the individual’s demands and situation. A 6 MV photon linear accelerator was the device used for external beam radiation treatment.

Radiation was applied in fractions of 1.8 Gy daily, five times a week up to a total of 50.4 Gy. In case of R1 resection, dosage was enhanced in the R1-margins area to 59.4 Gy. A vaginal brachytherapy (2 × 5 Gy) was additionally applied if R1 resection was in the vaginal stump.

Target volumes were the pelvic lymph nodes and the primary tumor area. In case of tumor involvement of the common iliac lymph nodes, the radiation field was expanded up to the 3/4 lumbar vertebral body.

In the case of any grade 3 or 4 toxicity according to the NCI-CTC [11] version 3.0.22, radiation was interrupted for at least 1 week.

end points

The primary objective of this study was to compare PFS between the two study arms in patients with high-risk CC after radical hysterectomy.

Secondary objectives included comparisons of time to treatment failure, overall survival (OS), toxicity profiles, localization sites of the relapse, interruptions of treatment schedules, hemoglobin levels and disease-specific quality of life (QoL). Toxicity data were collected and graded prospectively on study forms as the patients were treated in terms of severe adverse events. The instrument’s functional assessment of cancer therapy-cervix cancer (FACT-Cx) and functional assessment of cancer therapy-anemia (FACT-An) scales were used to assess health-related QoL (HRQoL). Qualities of life were assessed on study entry, as well as before the fourth chemotherapy cycle and before the last radiation session in arm-A and before the last radiochemotherapy cycle in arm-B.

eligible patients were included in the analysis of survival based on the intention-to-treat (ITT) principle.

All patients underwent a thorough clinical, imaging and laboratory examination 4 weeks after completion of radiation on radiochemotherapy, depending on which experimental arm was used for treatment. Follow-up was undertaken up to 5 years; every 3 months within the initial postoperative year and subsequently every 6 months. Response was determined according to RECIST [12].

statistical analysis

We planned a recruitment of 100 patients each year over a 3-year enrollment period and a 1-year additional follow-up. The sample size was calculated to detect a 40% benefit in PFS using log-rank test with \( P = 0.05 \) and power = 0.80. This calculation was based on the assumption that there is a meaningful difference between the proportions of patients without progression of disease at 2 years in the B and A-arms of 10% (85% versus 75%). In both arms, there was an equal number of patients and a dropout rate of 5%. However, only 271 patients were enrolled within 3.5 years, due to the decreased recruitment seen for 69 patients in the first year until 38 patients in the fourth year. A longer recruitment period reduces the number of patients needed, but the power may be reduced. Both groups were compared using the Chi-square test, Fisher’s exact test, Kendall’s tau-b and Mann-Whitney U test, where appropriate. Two-year PFS after randomization and 95% confidence interval (CI) were estimated according to the Kaplan–Meier method. Survival was calculated after randomization. For comparisons of PFS and OS, log-rank test was used. Adjusted hazard ratios (HRs) were estimated with the use of Cox regression analyses. QoL from baseline to the end of therapy was analyzed using general linear models. All analyses were carried out with PASW18.0 (SPSS Inc., Chicago, IL, 2009).

results

patients

Two hundred and ninety-one patients were registered from 1 April 2003 to 1 September 2008 (Figure 2). Of these patients, 271 were randomized. After randomization, eight patients were excluded due to missing inclusion criteria \((n = 3)\), present exclusion criteria \((n = 4)\) or other protocol violation \((n = 1)\). A total of 263 patients were clinically eligible for the study \((n = 132 \text{ in arm-A and } n = 131 \text{ in arm-B})\) and were included into the ITT analysis (ITT dataset). Of those, 12 patients did not receive the assigned study treatment or any other chemotherapy but were still included in the ITT analysis of primary and secondary outcomes as randomly assigned. Fifty-nine further patients did not complete therapy \((n = 17 \text{ in arm-A and } n = 42 \text{ in arm-B; } P = 0.001, \text{ log-rank test})\) but were included in the toxicity analysis as randomly assigned according to the ITT analysis among eligible patients. Both arms were well balanced regarding all patient and cancer-related characteristics (Table 1). Median intervals from surgery to start of treatment were 32 days (range: 15–104 days) and 45 days (19–139 days) in arm-A and B, respectively.

Nineteen patients (14.3%) failed to receive or to complete radiotherapy in arm-A and 21 patients (16%) in arm-B. Radiotherapy (RT) was not discontinued when chemotherapy had to be halted. Median duration, quartiles and range of radiation treatment was in arm-A: 39 days (25%: 37, 75%: 43, 104 days) and 45 days (19–139 days) in arm-A and B, respectively.
range: 0–71) and in arm-B: 39 days (25%: 37, 75%: 42, range: 0–76); *P* = 0.53 (log-rank test).

**efficacy**

Median follow-up was at 42.5 months (range: 0–75) in arm-A and 37 months (range: 0–79) in arm-B, which was not significantly different (*P* = 0.13, log-rank test). Twenty-six cases (19.7%) in arm-A and 32 cases (24.4%) in arm-B were censored 2 years in advance. Some of these cases were caused by study termination before reaching a follow-up of 2 years.

Sixteen (12.1%) patients (6 local, 3 local and distant, 7 distant) in arm-A and 25 (19.1%) patients (4 local, 1 local and distant, 20 distant) in arm-B experienced a recurrence (*P* = 0.013, log-rank test). Sixteen patients (12.1%) in the sequential arm and 20 patients (15.3%) in the simultaneous arm died during follow-up (*P* = 0.48, log-rank test). However, the observed HR of 0.48 provided for arm-A versus B contradicts the results of the primary analysis, which can be explained by the fact that the proportion of events to number of variables included is relatively small for this kind of analysis. Therefore, the results of this explorative analysis should be interpreted with caution since no prospective stratification was carried out.

PFS was not statistically significant different between patients in the sequential arm versus those in the simultaneous arm (*P* = 0.25, log-rank test). The 2-year PFS was 87.2% (95% CI 81.2–93.3) versus 81.8% (95% CI 74.4–89.1), respectively. The estimated 5-year OS for patients in the sequential versus simultaneous arm was 84.2% (95% CI 76.6–91.9) versus 77.4% (95% CI 68.3–86.4), respectively. Arm-A versus B (HR: 0.483; 95% CI 0.25–0.92; *P* = 0.028, log-rank test), increasing age (HR: 1.03; 95% CI 1.003–1.067; *P* = 0.034, log-rank test), tumor size ≥4 cm (HR: 7.77; 95% CI 1.042–57.995; *P* = 0.046, log-rank test) and positive lymph node status N1 (HR: 5.26; 95% CI 2.3–12.104; *P* < 0.001, log-rank test) were identified as having a statistically significant impact on PFS in multivariate analysis, even though negative in univariate analysis. Histological grading or type, tumor size 2–4 cm versus <2 cm and tumor resections margins did not appear to have any significant impact on PFS.

The 5-year OS for patients in the sequential versus simultaneous arm was 84.2% (95% CI 76.6–91.9) versus 77.4% (95% CI 68.3–86.4), respectively. Again, univariate analysis failed to demonstrate statistical significance (*P* = 0.34, log-rank test). Multivariate analysis did not identify the type of treatment (i.e. sequential versus simultaneous) as independent prognostic factor of survival (HR: 0.59; 95% CI 0.3–1.18; *P* = 0.137, log-rank test). In addition, tumor grading (G1/2 versus G3), histological type (squamous versus adenocarcinoma), tumor size (<4 versus ≥4 cm) and tumor resection margins (R0 versus R1) were not identified as significant prognosticators. Only increasing age (HR: 1.04; 95% CI 1.008–1.077; *P* = 0.15, log-rank test) and positive lymph node status (HR: 4.53; 95% CI 1.84–11.16; *P* = 0.001, log-rank test) were independent predictors affecting OS.

**adverse effects**

Two hundred and fifty-one patients were assessable for toxicity assessment. Figure 2 compares the frequency of adverse events between the two arms of the study. Significantly, more darbepoetin treatment was required in arm-A versus arm-B (87.5% versus 69.6%; *P* = 0.001, log-rank test), while this relation was reverse in the need of granulocyte colony-stimulating factor treatment (5% versus 15%; *P* = 0.01, log-rank test).
The sequential arm (A) appeared to have a significantly more favorable toxicity profile when compared with the simultaneous arm (B) regarding the rate of overall hematological toxicity (grade 3/4: 34% versus 48%; \(P = 0.028\), log-rank test), deep venous thrombosis (1.6% versus 6.5%; \(P = 0.047\), log-rank test) and vomiting (grade 1/2: 22.2% versus 36.9%; \(P = 0.01\), log-rank test). In contrast, more favorable values for the simultaneous arm were observed in terms of lower severe neutropenia (25.9% versus 9.5%; \(P < 0.001\)), grade 2 alopecia (87.9% versus 4.1%; \(P < 0.001\), log-rank test), grade 1/2 mucositis (28.6% versus 11.5%; \(P = 0.001\), log-rank test), grade 1/2 hand-foot syndrome (9.5% versus 2.5%; \(P = 0.03\), log-rank test), grade 1–3 arthralgia (46.8% versus 6.6%; \(P < 0.001\), log-rank test), grade 1–3 myalgia (41.3% versus 13.9%; \(P < 0.001\), log-rank test) and grade 1–3 neurotoxicity (65.9% versus 15.6%; \(P < 0.001\), log-rank test).

Regarding the acute radiation-related toxicity, the data offered here favor significantly the sequential arm in terms of lower grade 1/2 pain during radiation (9.3% versus 24.8%; \(P = 0.003\), log-rank test), grade 1–3 abdominal cramping (13.9% versus 34.7%; \(P < 0.001\), log-rank test) and grade 1/2 obstipation (4.6% versus 24.8%; \(P < 0.001\), log-rank test). Also grade 2/3 anorexia was lower in the sequential arm (1.9% versus 11.14%; \(P = 0.007\), log-rank test). No significant differences were noted between the two arms in regard to radiogenic dermatitis, dysuria, hematuria, mucositis, rectal bleeding, incontinence and as regard to long-term radiation-related adverse effects.

Reasons for withdrawal were in arm-A \((n = 17)\): patients’ wish: 5 (29.4%), progress: 1 (5.9%), arterial embolism of the arm: 1 (5.9%), leucopenia: 1 (5.9%), physicians decision: 1 (5.9%), allergy grade III: 1 (5.9%), neurological toxicity: 1 (5.9%), poor diabetic control: 1 (5.9%) and in arm-B \((n = 42)\) patients wish: 13 (31%), fever and myelosupression: 15 (35.7%), physicians’ decision: 2 (4.8%), protocol violation: 1 (2.4%), lost/no compliance: 2 (4.8%), gastrointestinal toxicity/diarrhea: 4 (9.5%), septic complication: 1 (2.4%), uncontrolled hypertension: 1 (2.4%), urinary problems: 1 (2.4%), thrombopenia: 1 (2.4%) and renal insufficiency: 1 (2.4%). Data are presented in supplemental Table S1 (available at Annals of Oncology online).

**Quality of life**

Mean FACT-Cx scores were constantly improving from the beginning toward the end of the treatment for all patients \((P = 0.04\), log-rank test\), regardless of the arm into which they were randomized. No significant changes were recorded regarding the FACT-An scores. Emotional well-being was on the average significantly better from the time of registration toward the end of therapy. Hereby, there were no significant differences between the two arms (supplemental Figure S2, available at Annals of Oncology online).

**Discussion**

This report summarizes a clinical trial comparing advantages and disadvantages of sequential versus simultaneous radiochemotherapy as adjuvant regime in high-risk CC. We could demonstrate significantly lower hematological toxicity and lower rates of deep venous thrombosis and vomiting in the sequential arm. In terms of acute radiological toxicity, the sequential arm was significantly beneficial in various aspects such as pain, abdominal cramping and obstipation. However, complaints of grade 1/2 pain and constipation in the simultaneous arm may in part relate to the fact that these patients had RT in much closer proximity to their surgery and were therefore more likely to be experiencing residual direct postoperative symptoms. Moreover, the sequential arm was associated with significantly higher rates of hair loss and neurotoxicity, whereas HRQoL scores were not significantly different between both arms.

Despite promising previous experiences that favored the combination regimes compared with single agent cisplatin in respect to both higher response and survival rates [6, 13], this study failed to demonstrate an amelioration of survival by the addition of paclitaxel to platinum in high-risk CC. Two-year PFS and OS rates did not significantly differ between the two arms. Nevertheless, the 26 disease-related events in this trial are not sufficient enough to support the results of multivariate analysis since the proportion of events to the number of variables included is relatively small for this kind of analysis. The results of this explorative analysis should therefore be interpreted with caution.

Furthermore, one has to consider a potential disadvantage of the sequential arm deriving from the prolonged time between radiation and surgery. Many studies in a variety of tumor types—particularly head and neck—have demonstrated poorer local control when RT is delayed or when the total ‘package time’ from surgery to completion of RT is prolonged [14].

There is evidence of a higher benefit of multiagent systemic chemotherapy over single agent regimes for advanced or high-risk CC [6, 13]. Nevertheless, the combination regimes appear to be associated with a significantly higher hematologic toxicity profile (e.g. 70% versus 1.4% grade 3/4 neutropenia), whereas an important difference between our current platinum/taxane regimen and the one applied in Gynecologic Oncology Group (GOG) 169 was that in GOG 169, both highly neurotoxic agents, cisplatin and paclitaxel, were administered. In our trial, we indeed showed that neurotoxicity was higher in the sequential arm; however, grade 2+ neurotoxicity rates were acceptable and not significantly higher.

Pectasides et al. [15] evaluated the activity and toxicity of the combination carboplatin and paclitaxel in 51 patients with advanced or recurrent CC who could also recently demonstrate that the combination regime has a considerable activity in this patients collective by an overall acceptable toxicity profile. These data reveal a clearly higher toxicity compared with our data; however, one has to consider that our patients collective presented only a locally restricted disease and had no prior myelotoxic therapies.

Interesting is the fact of the significant lower thrombosis rate in the sequential arm. This could be potentially attributed to the higher physical stress involving treatment in the combined regime and definitely sets the basis for further investigation.
patients with additional high thromboembolic risk profile, the sequential regime could thus constitute a reasonable alternative treatment due to its lower thrombogenic risk. The same applies to patients with local secondary wound healing problems, where immediate local radiotherapy would constitute a problem by impairing healing.

The increased rates of venous thrombosis and vomiting with concurrent chemotherapy/radiation therapy may be based on the manner in which the study was conducted. The increased risk of venous thrombosis during chemoradiation for CC in GOG 191 led to termination of the study in September 2003. Subsequently, the Food and Drug Administration issued a ‘black box warning’ regarding the increased risk of life-threatening thrombosis. Additionally, the rate of cisplatin administration is up to twice as fast as the administration used in the GOG trials. It is well known that the rate of cisplatin administration is related to its emetogenic effect, and it is likely which led to the high rates of nausea and vomiting seen in the radiation/cisplatin arm.

In conclusion, we could show that even though we failed to assess a survival benefit of the experimental regimen, toxicity profile and tolerability appear to favor the use of a sequential strategy of systemic chemotherapy followed by radiation in high-risk CC in regard to radiation-related toxicity. However, a different type of toxicity profile related to hair loss and neurotoxicity emerges, which definitely has to be discussed individually with the affected patients.

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disclosure
The authors declare no conflict of interest.

references