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Thieme

Statement of the Uterus Commission of the Gynecological Oncology Working Group (AGO) on Neoadjuvant Chemotherapy Prior to Definitive Radiochemotherapy in Patients with Locally Advanced Cervical Cancer

Stellungnahme der Kommission Uterus der Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) zur neoadjuvanten Chemotherapie vor definitiver Radiochemotherapie bei Patientinnen mit lokal fortgeschrittenem Zervixkarzinom

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ABSTRACT

The presentation of the results of the prospective randomized international multicenter GCIG INTERLACE trial at the 2023 congress of the European Society of Medical Oncology (ESMO) is likely to change the therapy for locally advanced cervical cancer. In the GCIG INTERLACE trial, six cycles of neoadjuvant chemotherapy administered weekly and consisting of carboplatin AUC2 and paclitaxel 80 mg/m^2 followed by definitive radiochemotherapy with pelvic radiotherapy (40–50.4 Gray) and cisplatin (40 mg/m^2 once a week for 5 weeks) and brachytherapy (total dose EQD2 at least 78 Gy at point A) (experimental arm) were compared with definitive radiochemotherapy alone (standard arm) in patients with locally advanced cervical cancer (Fédération Internationale de Gynécologie et d'Obstétrique [FIGO] 2008 stage IB1/node positive, IB2, II, IIIB and IVA) and was found to be significantly superior with significantly longer recurrence-free survival (hazard ratio [HR] 0.65; 95% confidence interval [CI] 0.64–0.91; p = 0.013) and significantly longer overall survival rates (HR 0.61; 95% CI: 0.40–0.91; p = 0.04) after 5 years' follow-up. After considering the results of the GCIG INTERLACE trial published at the congress, the Uterus Commission of the AGO is of the opinion that neoadjuvant chemotherapy with carboplatin AUC2 and paclitaxel 80 mg/m^2 d1, q7, x6 may be offered to patients with locally advanced cervical cancer (FIGO stage IB1/node positive, IB2, II, IIIB and IVA) in addition to the current standard therapy after the patient has been informed about the risks, with the decision taken on a case-by-case basis. However, before this approach can be discussed at guideline level or defined as the new therapy standard, it will be necessary to wait until the data from the full publication are available.

ZUSAMMENFASSUNG

Die Präsentation der Ergebnisse der prospektiv-randomisierten internationalen Multicenterstudie GCIG-INTERLACE auf dem Kongress der European Society of Medical Oncology (ESMO) 2023 wird vermutlich die Therapie des lokal fortgeschrittenen Zervixkarzinoms verändern. In der GCIG-INTERLACE-Studie waren 6 Zyklen einer wöchentlichen neoadjuvanten Chemotherapie mit Carboplatin AUC2 und Paclitaxel 80 mg/m^2 gefolgt von einer definitiven Radiochemotherapie mit Beckenbestrahlung (40–50,4 Gray) und Cisplatin (40 mg/m^2 wöchentlich für 5 Wochen) sowie Brachytherapie (Gesamtdosis EQD2 mindestes 78 Gy an Punkt A) (experimenteller Arm) gegenüber einer alleinigen definitiven Radiochemotherapie (Standardarm) bei Patientinnen mit lokal fortgeschrittenem Zervixkarzinom mit Fédération Internationale de Gynécologie et d'Obstétrique (FIGO)-2008-Stadien IB1/nodal positiv, IB2, II, IIIB und IVA signifikant überlegen und führten nach 5 Jahren Nachbeobachtungszeit zu einem signifikant verlängerten rezidivfreien Überleben (Hazard Ratio [HR] 0,65; 95%-Konfidenzintervall [KI] 0,64–0,91; p = 0,013) und einem signifikant verlängerten Gesamtüberleben (HR 0,61; 95%-KI 0,40–0,91; p = 0,04). In Abwägung der auf dem Kongress publizierten Ergebnisse der GCIG-INTERLACE-Studie kann daher nach Einschätzung der Organkommission Uterus der AGO e.V. bei Patientinnen mit lokal fortgeschrittenem Zervixkarzinom der FIGO-Stadien IB1/nodal positiv, IB2, II, IIIB und IVA zusätzlich zur bisherigen Standardtherapie nach entsprechender Risikoaufklärung im Sinne einer Einzelfallentscheidung eine neoadjuvante Chemotherapie mit Carboplatin AUC2 und Paclitaxel 80 mg/m^2 d1, q7, x6 angeboten werden. Die Daten der Vollpublikation müssen allerdings abgewartet werden, bevor dieses Vorgehen auf Leitlinienebene diskutiert und eventuell als neuer Therapiestandard definiert werden kann.

Introduction

The presentation of the results of the international randomized multicenter GCIG INTERLACE trial has expanded the clinical study landscape of primary therapy to treat patients with locally advanced cervical cancer (FIGO stage IB1/node positive, IB2, II, IIIB and IVA) [1]. For the first time, a prospective randomized study was able to show that induction therapy consisting of neoadjuvant chemotherapy administered prior to definitive radiochemotherapy results in a significant improvement in both recurrence-free survival and and overall survival without significantly increasing toxicity. Conincidentally, the results of the KEYNOTE-A18 trial were presented in October 2023. In the KEYNOTE-A18 trial, the addition of 5 cycles of pembrolizumab 200 mg d1, q21 to standard radiochemotherapy with adjuvant continuation of pembrolizumab for 15 cycles significantly prolonged recurrence-free survival in patients with locally advanced cervical cancer (HR 0.70; 95% CI: 0.55–0.89; p = 0.002) [2]. The current recommended standard therapy to treat locally advanced cervical cancer is summarized and presented below, followed by the results of the GCIG INTERLACE trial, which are interpreted and contextualized.

Current Recommendations to Treat Locally Advanced Cervical Cancer

The current S3-guideline from March 2022 on the therapy and follow-up of patients with cervical cancer recommends definitive radiochemotherapy to treat cases with locally advanced cervical cancer, (FIGO stage IB2 to III). For patients with FIGO stage IVA disease, the decision should be made on a case-by-case basis after an interdisciplinary consultation due to the high risk of fistula formation [3]. Primary radiochemotherapy consists of a combination of intensity-modulated pelvic radiotherapy and, in cases with positive paraaortic lymph nodes, extended field radiation which includes the paraaortic region with a total dose of 45–50.4 Gray or 50 Gray, combined with magnetic resonance imaging (MRI)-guided brachytherapy administered at a high dose rate (HDR) or pulse dose rate (PDR) up to a cumulative biologically equivalent dose (EQD2) of 80–90 Gy in the tumor as well as concomitant weekly chemotherapy with cisplatin for 5 weeks consisting of 5–6 doses of 40 mg/m^2 on days 1, 8, 15, 22, 29, and poss. 36 of radiotherapy [3]. Neoadjuvant chemotherapy is currently not rec-

ommended as part of the standard therapy for patients with locally advanced cervical cancer. Specifically, with regards to the issue of neoadjuvant chemotherapy, the guideline states that neoadjuvant chemotherapy may only be administered as a possible treatment alternative to selected high-risk patients to shrink the tumor prior to planned surgical therapy [3]. The basis for this recommendation is a meta-analysis of 739 patients from randomized RCTs which included patients with FIGO stage IB1–III cervical cancer. The meta-analysis found no positive effect of neoadjuvant chemotherapy with regards to overall survival (odds ratio [OR] 1.17, 95% CI: 0.85–1.61; p = 0.35) or disease-free survival (OR 1.09, 95% CI: 0.77–1.56; p = 0.62) [4]. However, it did find a significant reduction in the rate of lymph node metastasis (OR 0 : 45, 95% CI: 0.29–0.7; p = 0.0005) and parametrial infiltration (OR 0.48, 95% CI: 0.25–0.92; p = 0.03) which corresponded to downstaging. As regards neoadjuvant chemotherapy, the guideline generally states that it should currently not be administered outside clinical trials [3]. The guideline discusses the meta-analysis and refers specifically to the heterogeneous treatment concepts for neoadjuvant chemotherapy and radiochemotherapy, the differences in patient groups, tumor stages, treatment concepts, radiotherapy techniques and dosages and the different chemotherapy regimens [3]. Although promising response rates were observed, none of the studies to date were able to show a clear benefit with regards to overall or disease-free survival compared with standard radiochemotherapy or primary radical surgery [4]. As regards the specific issue of neoadjuvant chemotherapy prior to primary definitive radiochemotherapy, the guideline states that no advantage has been demonstrated in previous publications and that this therapy can therefore not be recommended. The guideline also specifically references the early results of a randomized study with just 80 patients which compared the response rates in both arms (radiochemotherapy plus/minus neoadjuvant chemotherapy), although the oncological endpoints have not yet been published [5]. Im summary, as no benefits were demonstrated, the guideline recommends, based on the data available up until 2022, that the concept of neoadjuvant chemotherapy prior to definitive radiochemotherapy should not be administered outside clinical trials [3].

Previous Literature on Chemotherapy for Locally Advanced Cervical Cancer

The concept of adding neoadjuvant or additive chemotherapy to primary radiochemotherapy has already been investigated in several studies using different approaches. One prominent example was the OUTBACK trial, a large prospective randomized Australian study of 926 patients with locally advanced cervical cancer (FIGO 2008 stages IB1, N+, II, III, and IVA) [6]. The study was a comparison of primary radiochemotherapy including pelvic radiotherapy and brachytherapy and 5 × cisplatin 40 mg/m^2 with or without the addition of sequential chemotherapy with 4 cycles of carboplatin AUC5 and paclitaxel 155 mg/m^2 d1, q21. No improvement in survival was found after 5 years for the experimental arm of the study (overall survival rate of 72%; 95% CI: 67% – 76%) compared to the standard arm (overall survival rate of 71%; 95% CI: 66% – 75%). As expected, the toxicity in the experimental group was higher (myelotoxicity of 20% versus 8%; anemia was 18% versus 8%). In contrast to the OUTBACK trial, the study published by Duenas-Gonzales et al. found that chemotherapy-sensitizing with cisplatin and gemcitabine during primary radiochemotherapy, followed by additional adjuvant chemotherapy with cisplatin and gemcitabine, offered better results with regards to 3-year recurrence-free survival and overall survival than radiochemotherapy alone with just cisplatin [7]. Duenas-Gonzales et al. specifically randomized 515 patients with locally advanced cervical cancer (FIGO stages IIB to IVA) into two arms: radiochemotherapy with pelvic radiotherapy and 6 × cisplatin 40 mg/m^2 and gemcitabine 125 mg/m^2 administered weekly, followed by brachytherapy and adjuvant chemotherapy with 2 × cisplatin 50 mg/m^2 and gemcitabine 1200 mg/m^2 d1, 8, q21 versus standard therapy (radiochemotherapy with cisplatin 40 mg/m^2). The experimental arm had a longer 3-year recurrence-free survival rate of 74% compared to 65% (p = 0.029) and a longer 3-year overall survival rate (HR 0.68, 95% CI: 0.49–0.95; p = 0.022) but this was accompanied by an intolerable increase in toxicity in the experimental arm (grade 3/4 toxicities in 86% versus 46% including 2 toxicity-related deaths). Because of the significant toxicity, this approach did not gain international acceptance.

A smaller randomized phase II study of 107 patients with locally advanced cervical cancer (FIGO stages IIB to IVA) showed no improvement with regards to 3-year recurrence-free survival and overall survival compared to neoadjuvant chemotherapy with cisplatin and gemcitabine followed by primary radiochemotherapy versus radiochemotherapy alone [8].

The Chinese STARS trial recorded a positive effect for chemotherapy combined with radiochemotherapy with regards to recurrence-free survival, however only in a purely adjuvant context following surgery [9]. This 3-arm prospective randomized trial of 1048 patients with FIGO stage IB–IIA disease and additional risk factors who underwent radical hysterectomy compared adjuvant radiotherapy with adjuvant radiochemotherapy and adjuvant "sandwich" therapy consisting of 2 cycles of cisplatin 60–75 mg/m^2 and paclitaxel 135–175 mg/m^2 d1, q21, followed by pelvic radiotherapy, followed by a further 2 cycles of cisplatin 60–75 mg/m^2 and paclitaxel 135–175 mg/m^2 d1, q21. This study reported a better 3-year recurrence-free survival rate in the sandwich group compared to both other arms (90% versus 82% after adjuvant radiotherapy [HR 0.52, 95% CI: 0.35–0.76] and 90% versus 85% [HR 0.65, 95% CI: 0.44–0.96] after adjuvant radiochemotherapy). Because this study used a purely adjuvant postoperative approach, it is not relevant when considering the issue of neoadjuvant chemotherapy prior to primary radiochemotherapy, but it does emphasize the potential importance of a combination of systemic chemotherapy and radiotherapy.

Overall, none of the studies published in the last 15 years were able to establish a viable concept for neoadjuvant chemotherapy followed by primary radiochemotherapy. This is why primary radiochemotherapy with cisplatin 40 mg/m^2 as a radiotherapy sensitizer has remained the international therapy standard up until the present when treating patients with locally advanced cervical cancer.

Neoadjuvant Chemotherapy with Cisplatin and Paclitaxel for Locally Advanced Cervical Cancer: the GCIG-INTERLACE Trial

Despite many years of clinical research and various investigations into therapy concepts, it proved impossible to develop a viable concept for neoadjuvant chemotherapy prior to primary radiochemotherapy to treat patients with locally advanced cervical cancer. Data from randomized trials were previously lacking, were negative, or demonstrated excessively high toxicity. With the GCIG INTERLACE trial we now have the first prospective randomized study on this issue with a positive and viable therapy concept. Based on the results of a phase II study, Mc Cormack et al. developed a concept consisting of weekly dose-dense neoadjuvant chemotherapy with cisplatin and paclitaxel [10]. In this one-arm study of 46 patients with FIGO stage IB2 to IVA cervical cancer, the weekly administration of carboplatin AUC2 and paclitaxel 80 mg/m^2 d1, q7 x6 resulted in complete or partial response in 70% after neoadjuvant chemotherapy and in 85% after completion of radiochemotherapy; the toxicity was tolerable (grade 3/4 toxicity in 20% during the neoadjuvant phase). The overall survival rate and the progression-free survival rate after 39 months was 67% and 68%, respectively. The study concept of the GCIG INTERLACE trial was developed base d on these data.

The GCIG INTERLACE trial is an international multicenter trial. The trial has investigated outcomes after definitive primary radiochemotherapy with pelvic radiotherapy (40–50.4 Gy in 20 to 28 fractions) and cisplatin (40 mg/m^2 weekly for 5 weeks) and brachytherapy (minimum total dose of 78 Gy) (standard arm) in patients with locally advanced cervical cancer (Fédération Internationale de Gynécologie et d'Obstétrique [FIGO] 2008 stage IB1/node positive, IB2, II, IIIB, IVA) compared with outcomes in the experimental arm where patients received six cycles of weekly neoadjuvant chemotherapy with carboplatin AUC2 and paclitaxel 80 mg/m^2, immediately followed by definitive radiochemotherapy and brachytherapy in the 7th week of therapy. Patients with squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma of the uterine cervix were also included. No enlarged lymph nodes and/or lymph nodes suspicious for metastasis above the aortic bifurcation detectable on imaging were included. The duration of treatment was limited to 50 days; image-guided adaptive brachytherapy was additionally recommended. All centers were subject to a radiotherapy quality assurance program. Follow-up consisted of controls every 3 months for the first 2 years, then controls every 6 months for a total of 5 years. The two primary endpoints of the study were progression-free survival and overall survival after 5 years. In the sample size calculation the study, which had 500 participants, was found to have a power of 84% for the endpoint "overall survival".

Results of the GCIG INTERLACE Trial

The most important patient characteristics of this study were: mean patient age of 46 years; FIGO stage IIB: 70% and 71%, respectively; FIGO stage IIIB: 12% and 10%, respectively; squamous cell carcinoma: 82% and 82%, respectively; node positive: 43% and 42%, respectively. ▶ **Table 1** provides a summary of the patient characteristics of the GCIG INTERLACE trial. 84% of patients who received neoadjuvant chemotherapy adhered to therapy and received all 6 cycles. Adherence to cisplatin therapy during radiotherapy was lower in the experimental arm with 68% of patients adhering to therapy compared to 79%. The mean duration of treatment for both arms was 45 days.

▶ **Table 1** Summary of patient characteristics in the GCIG INTERLACE trial [1].

Factors	Primary radio-chemotherapy (n [%])	NACT + primary radiochemo-therapy (n [%])
FIGO (2008) stage		
IB1	2 (< 1)	2 (< 1)
IB2	23 (9)	19 (8)
IIA	14 (6)	17 (7)
IIB	176 (70)	178 (71)
IIIB	30 (12)	26 (10)
IVA	5 (2)	8 (3)
Histological type		
squamous	205 (82)	206 (82)
non-squamous	45 (18)	44 (18)
Lymph node status		
positive	108 (43)	104 (42)
negative	142 (57)	146 (58)
Maximum tumor diameter (cm)		
residual tumor (cervix)	4.9 (1.8–12.8)	4.8 (1.3–13.5)
ECOG status		
0	221 (88)	214 (86)
1	29 (12)	36 (14)

Abbreviations: NACT = neoadjuvant chemotherapy; ECOG = Eastern Cooperative Oncology Group

With regards to the primary endpoints, the results of the GCIG INTERLACE trial confirm the study hypothesis that weekly neoadjuvant chemotherapy prior to definitive radiochemotherapy & brachytherapy is superior to definitive radiochemotherapy & brachytherapy alone in a patient cohort with locally advanced cervical cancer. Six cycles of weekly neoadjuvant chemotherapy with carboplatin AUC2 and paclitaxel 80 mg/m^2 followed by definitive radiochemotherapy & brachytherapy (experimental arm) were found to be significantly superior at a clinically relevant level compared to definitive radiochemotherapy & brachytherapy (standard arm) after 5 years of follow-up with regards to overall survival and recurrence-free survival. Specifically, there were 70 cases with recurrence in the experimental arm as opposed to 91 cases with recurrence in the standard arm. This effect was achieved exclusively through reducing distant metastasis (30 versus 50 cases; 12% vs. 20%), whereas local recurrence was approximately the same in both arms (40 versus 41 cases). After 5 years, the difference between groups with regards to the recurrence-free survival rate was 9% (HR 0.65, 95% CI: 0.46–0.91; p = 0.013) and 8% with re-

▶ **Table 2** Recurrence and survival data of the GCIG INTERLACE trial [1].

Endpoints	Primary radiochemotherapy	NACT + primary radiochemotherapy		
	5-year outcome		HR (95% CI)	p-value
Local/pelvic recurrence	41 (16%)	40 (16%)	–	–
Extrapelvic recurrence	50 (20%)	30 (12%)	–	–
Recurrence-free survival	64%	73%	0.65 (0.46–0.91)	0.013
Overall survival	72%	80%	0.61 (0.40–0.91)	0.04

gards to the overall survival rate (HR 0.61, 95% CI: 0.40–0.91; p = 0.04). The 3-year overall survival rate was 80% (standard arm) versus 86% (experimental arm), and the 5-year overall survival rate was 72% (standard arm) versus 80% (experimental arm). The 3-year recurrence-free survival rate was 72% (standard arm) versus 75% (experimental arm), and the 5-year recurrence-free survival rate was 64% (standard arm) versus 73% (experimental arm). The data on survival are summarized in ▶ **Table 2**.

Toxicity

The addition of neoadjuvant combination chemotherapy with carboplatin and paclitaxel resulted in a moderate increase in the toxicity of primary radiochemotherapy, primarily through an increase in myelotoxicity. The overall rate of adverse events in the experimental arm was only 4% higher (95% versus 99%). The difference in grade 3/4 events was 11% (48% versus 59%). As expected, the biggest difference was found for hematological parameters (13% versus 30% with regards to all hematotoxic events). This particularly applied to neutropenia (19% versus 5%); the difference was less pronounced for anemia and thrombocytopenia (5% versus 4% and 5% versus 2%, respectively). Non-hematotoxic adverse events were approximately the same in both arms of the study (44% versus 43%). Overall, it can be stated that the addition of neoadjuvant chemotherapy did not result in a limiting increase in toxicity. This is an indication for the viability of the therapeutic concept investigated in the GCIG INTERLACE trial.

Final Appraisal and Treatment Recommendation

At present, the results of the prospective randomized international multicenter GCIG INTERLACE trial on the addition of neoadjuvant chemotherapy to treat patients with locally advanced cervical cancer are only availble as an abstract and a conference presentation. The results indicate that the addition of neoadjuvant chemotherapy can lead to a statistically significant and clinically relevant improvement in both recurrence-free survival and overall survival. This would represent a new therapy alternative to the current standard therapy which consists of radiochemotherapy alone. Specifically, it was found that the addition of 6 neoadjuvant cycles of carboplatin AUC2 and paclitaxel 80 mg/m^2 resulted in

1. **significantly improved 3-year and 5-year overall survival rates,**
2. **significantly improved 3-year and 5-year recurrence-free survival rates,**
3. **a numerical reduction in the rate of extrapelvic recurrence,**
4. **no numerical reduction in the rate of local/pelvic recurrence, and**
5. **significantly higher myelotoxicity.**

The results of the GCIG INTERLACE trial suggest that neoadjuvant combination chemotherapy administered weekly significantly increases the efficacy of radiochemotherapy & brachytherapy.

Nevertheless, it is important to mention some points and aspects which will possibly only be resolved when study is published in full.

1. Patients with enlarged or suspicious lymph nodes on imaging above the aortic bifurcation were excluded from the study. It is important to know what the percentage was of patients who had surgical staging of the pelvis and (in cases with positive pelvic lymph nodes) of the paraaortic region and how many patients' paraaortic region was only evaluated with imaging.
2. It is also important to determine whether patients with FIGO stage IB disease who are node positive underwent sentinel lymphadenectomy and whether these patients underwent systematic pelvic lymphadenectomy and, where necessary, paraaortic lymphadenectomy.
3. The numerical rate of extrapelvic recurrence was significantly lower in the experimental arm but the rate of pelvic recurrences did not decrease. This appears to indicate that neoadjuvant chemotherapy only affects distant metastasis and that the efficacy might be limited to a subgroup of poorly differentiated and/or node-positive tumors. A subgroup analysis on this point would be useful.

Conclusion

The results of the GCIG INTERLACE trial suggest that neoadjuvant combination chemotherapy with carboplatin and paclitaxel followed by radiochemotherapy & brachytherapy is significantly superior to the current standard which consists of radiochemotherapy & brachytherapy alone to treat patients with locally advanced cervical cancer (FIGO 2008 stages IB1/node positive, IB2, II, IIIB, IVA) and that therefore this new approach may be discussed with affected patients on a case-by-case basis as an alternative to the

current standard therapy. The benefits of adding neoadjuvant chemotherapy are an improvement in recurrence-free survival and overall survival. The decision to add neoadjuvant chemotherapy in individual cases must not jeopardize the subsequent administration of radiochemotherapy. Around one in 12 patients benefitted from neoadjuvant chemotherapy. It will be necessary to wait until the data of the full publication of the GCIG INTERLACE trial are available before this approach can be discussed at the level of guidelines and and possibly defined as a new therapy standard. The Uterus Commission of the AGO is of the opinion that neoadjuvant chemotherapy followed by radiochemotherapy & brachytherapy may currently be offered to affected patients with the decision taken on a case-by-case basis after the patient has been informed about the risks involved.

Conflict of Interest

The authors state that they have no conflict of interest.

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