Outcomes after cisplatin alone or in combination regimens versus hydroxyurea during pelvic irradiation for cervical cancer

Dirk Rades and Steven Schild

Cisplatin-based chemoradiation has been shown to be superior to radiotherapy plus hydroxyurea for stage IB to III cervical cancer, conferring better survival rates with modest long-term toxicity.

Almost 10 years ago, five randomised trials that included almost 1,800 patients demonstrated a survival benefit of 30%–50% for cisplatin-based chemoradiation compared with radiotherapy alone in patients with locally advanced cancer of the cervix. After an initiative of the National Cancer Institute, two to six times more patients in the US received chemoradiation than before the initiative, resulting in improved survival in these patients. Despite these findings, many oncologists are still concerned about the efficacy and toxicity of cisplatin-based chemoradiation.

On the basis of the RTOG-9001 trial, one may question whether cisplatin-based chemoradiation is superior to radiotherapy alone for all stages of disease from IB to IVA.[1] The trial compared pelvic irradiation plus chemotherapy (cisplatin+5-fluorouracil) to irradiation of only the pelvic and para-aortic lymph nodes. The original report published in 1999 demonstrated a significant survival benefit for stage IB/II tumours (n=273), but not for stage III/IVA (n=116) tumours. The results were confirmed in the long-term analysis, which included 228 survivors and had a median follow up of 6.6 years.[2] In comparison with radiotherapy alone, chemoradiation resulted in improved overall survival (41% vs 67% at 8 years; P<0.001), disease-free survival (36% vs 61%; P<0.001), and loco-regional control (65% vs 82%; P<0.001).[2] Grade 3–4 late toxicity was reported as 14% in each group (P=0.50). A subgroup analysis revealed that the benefit of combined therapy was limited to patients with stage IB/II disease (P<0.001 for all end points). For those with stage III/IVA disease, only a trend towards improved outcome was observed (overall survival, P=0.07; disease-free survival, P=0.05; loco-regional control, P=0.065), a result that was most likely attributable to the relatively small number of patients in this subgroup.

The long-term results of the RTOG-9001 trial encouraged Rose et al. to evaluate the long-term results of their trial, GOG-120 (see opposite), particularly because the number of patients with International Federation of Gynecology and Obstetrics (FIGO) stage III tumours enrolled in this trial was comparatively large (n=234, 45%).[3] Indeed, concurrent cisplatin-based chemotherapy was associated with

Dirk Rades is associate professor of radiation oncology, and vice chair of the Department of Radiation Oncology, at the University Hospital Schleswig-Holstein, Lübeck, Germany, and Steven Schild is professor of radiation oncology, and vice chair of the Department of Radiation Oncology, at the Mayo Clinic, Scottsdale, Arizona, USA. This article was first published in *Nature Clinical Practice Oncology* 2008 vol. 5 no. 3, and is reproduced with permission. www.nature.com/clinical practice, doi:10.1038/ncponc1017,

significantly improved overall survival (OS) and progression-free survival (PFS) compared with radiotherapy plus hydroxyurea. Both 5-year and 10-year OS rates were increased by 20%. The survival benefit conferred by concurrent cisplatin-based chemotherapy in cervical cancer is much higher than that conferred by adjuvant chemotherapy in patients with breast cancer. Furthermore, the long-term results of the GOG-120 trial demonstrate that the survival benefit is not intermediate but long lasting (at least 10 years), with modest late toxicity (less than 5% grade 3–4 toxicity).

Two of the three other trials (besides RTOG-9001 and GOG-120) that favoured cisplatin-based chemoradiation for locally advanced cervical cancer included only patients with stage IB2, IB or IIA tumours. The third study included stage III/IV tumours, but no stage-related subgroup analyses. The GOG-120 trial is the only study that allows conclusions to be drawn regarding the value of cisplatin-based chemotherapy for stage III cervical cancer.[3] Future investigations will be needed to clarify the potential benefits of newer systemic agents and the role of cisplatin-based chemotherapy for stage IVA disease.

Details of the references cited in this article can be accessed at www.cancerworld.org/magazine

Synopsis

Peter G. Rose, Shamshad Ali, Edwin Watkins et al. (2007) **Long-term follow-up of a randomized trial comparing concurrent single agent cisplatin, cisplatin-based combination chemotherapy, or hydroxyurea during pelvic irradiation for locally advanced cervical cancer: a Gynecologic Oncology Group study.** *J Clin Oncol 25:2804–2810*

Background. The Gynecologic Oncology Group (GOG) protocol was the second of five randomised trials that examined the long-term outcomes associated with simultaneous cisplatin-based chemotherapy and pelvic irradiation for various stages of cervical cancer. Long-term results have been published for the trials.

Objective. To compare the long-term survival rates and toxicities associated with cisplatin-based chemotherapy and pelvic irradiation with those associated with hydroxyurea and concurrent pelvic irradiation in patients with locally advanced cervical cancer.

Design. This randomised phase III study included patients with untreated, stage IIB, stage III or stage IVA invasive squamous, adenosquamous or adenocarcinoma of the cervix. Eligible patients had a GOG performance status of 0, 1, 2 or 3, and normal haematologic, hepatic and renal function with no history of other malignancy. Patients with para-aortic node metastasis, intraperitoneal disease or disease outside the pelvis were not eligible for inclusion.

Intervention. Patients were randomly allocated to one of three chemotherapy regimens: cisplatin (40 mg/m^2 for 4 hours before irradiation on days 1, 8, 15, 22, 29 and 36); combined cisplatin (comprising cisplatin 50 mg/m^2 for 4 hours before irradiation on days 1 and 29, fluorouracil 4 g/m^2 as 96-hour infusions starting on days 1 and 29, and hydroxyurea 2 g/m^2 bi-weekly for 2 hours before radiation on weeks 1–6); or hydroxyurea (3 g/m^2 bi-weekly for 2 hours before radiation on weeks 1–6) alone. All chemotherapy regimens were delivered during external irradiation treatment. Pelvic irradiation was delivered at a dose of 1.7 Gy fractions to all patients, with a total dose of 40.8 Gy being given to patients with stage IIB and 51.0 Gy to patients with stage IIIB/IVA disease.

Outcome measures. The primary outcomes were progression-free survival (PFS) and overall survival (OS). Toxicity was a secondary outcome.

Results. During the period 1992–1997, 575 patients enrolled in the study, of whom 49 were ineligible, leaving a total study population of 526 patients. For surviving patients, the median follow-up time was 106 months. At 30 months' follow-up, PFS rates were 63% for the cisplatin regimen, 63% for the cisplatin-combination regimen and 42% for hydroxyurea alone. The corresponding PFS rates at 60 months and 120 months were 58%, 57% and 35%, and 46%, 43% and 26%, respectively. OS rates at 30 months were 70% in the cisplatin group, 70% in the cisplatin-combination group and 53% in the hydroxyurea group. At 60 months and 120 months, the corresponding rates of OS were 60%, 61% and 40%, and 53%, 53% and 34%, respectively. The relative risks of disease progression or death for the cisplatin regimen and the cisplatin-combination regimen in comparison with the hydroxyurea regimen were 0.57 and 0.51, respectively. In total, 518 patients received radiation. Acute urologic or gastrointestinal toxicities occurred in 66 patients in the cisplatin group (19.1%) and in 29 patients in the hydroxyurea group (16.8%).

Conclusion. Cisplatin-based chemotherapy during pelvic radiation improves long-term OS and PFS of patients with locally advanced cervical cancer, with acceptable acute and late toxicity.

Acknowledgement: The synopsis was written by Mandy Aujla, Associate Editor, *Nature Clinical Practice*.