Concurrent Cisplatin-Based Radiotherapy and Chemotherapy for Locally Advanced Cervical Cancer

Reviewers: Kenneth Blank, MD
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Introduction
The treatment of women with locally advanced cervical cancer is evolving. Radiotherapy and chemotherapy form the standard of care in the United States; however, the optimal type of chemotherapy is controversial. Traditionally, hydroxyurea has been the agent used concurrently with radiation; compared to radiotherapy alone, it significantly increases the likelihood of obtaining a complete response and prolongs overall survival. However, Phase I and II trials have indicated that cisplatin, with or without fluorouracil, may be more effective than hydroxyurea. To evaluate the optimal chemotherapy regimen for locally advanced cervical cancer, the Gynecologic Oncology Group (GOG) instituted a trial randomizing patients to one of three chemotherapy regimens given concurrently with radiotherapy. The three study arms were 1) weekly cisplatin 2) cisplatin, hydroxyurea and fluorouracil, 3) hydroxyurea. The results of this trial were reported in the April 15, 1999 issue of the New England Journal of Medicine.

Materials and Methods
575 patients with stage IIB (extension to the parametria), III (extension to the pelvic side wall) and IVA (involvement of bladder or rectum) were enrolled between 1992 and 1997. All tumors were histologically confirmed by the GOG pathology committee to be either squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma. All patients underwent an extraperitoneal lymph node biopsy and had to be pathologically para-aortic lymph node negative, have a GOG performance status of 3 or less, and have no history of treatment of cervical cancer or have had other cancers.

Patients were treated with megavoltage radiotherapy using anterior-posterior fields or a four field box technique. The upper border was L5 and the lower border was set at the mid-obturator foramen. Laterally the entire bony pelvis was included. If lateral fields were used, the anterior border was at the anterior edge of the pubic symphysis and the posterior border at the S2/3 interspace. The fields were modified to ensure coverage of the tumor. One to three weeks following external beam radiotherapy, one or two intracavitary placements were undertaken to deliver a total dose to point A of 80.8Gy in stage IIB and 81.0Gy in stage III or IVA. The total time of radiotherapy was 10 weeks.

Patients were randomly assigned to receive one of three chemotherapy regimens, all of which were dosed concurrent with radiotherapy: Group 1- cisplatin alone (40mg per square meter of body surface area, weekly for six weeks); Group 2- cisplatin (50mg per square meter body surface area on days 1 and 29), fluorouracil (4g per square meter of body surface area given as a 96-hour infusion on days 1 and 29) and hydroxyurea (2g per square meter of body surface area, twice weekly for six weeks); Group 3- hydroxyurea (3g per square meter of body surface area, twice weekly for six weeks).

Results
Forty-nine patients were excluded from the analysis. Of these 90% were for inadequate para-aortic lymph node dissection, leaving 526 patients: 176 in the group given radiotherapy and cisplatin (group 1); 173 in the group given radiotherapy and cisplatin, fluorouracil and hydroxyurea (group 2); and 177 in the group given radiotherapy and hydroxyurea (group 3). The median duration of follow-up was 35 months.

Overall survival and progression free survival were significantly improved in the patients receiving cisplatin chemotherapy (groups 1 and 2). Thirty-nine percent of all patients in the study had died: 59(33%) in group1, 57 (33%) in group 2 and 89 (50%) in group 3. The relative risk of death was 0.61 and 0.58 in groups 1 and 2, respectively, compared to group3. Approximately two-thirds of the patients in the two cisplatin groups were free from disease progression at two years compared to half of those in the hydroxyurea group. Analysis of patterns of failure revealed that cisplatin lowered the rate of local progression (20 percent...
versus 30 percent).

The frequency of grades three and four adverse effects was significantly increased on the three-drug arm of this study. The rate of grade three or four leukopenia in the group given radiotherapy combined with treatment with cisplatin, fluorouracil, and hydroxyurea was more than double the frequencies in the patients receiving cisplatin or hydroxyurea alone. There were no treatment-related deaths.

Conclusions
Cisplatin-based chemotherapy is superior to hydroxyurea in the treatment of women with locally advanced cervical cancer. There was no difference in progression free survival or overall survival between cisplatin alone and the three drug regimen, but the latter had a higher rate of toxicity, especially hematologic. Therefore, the authors recommend weekly cisplatin given concurrent with radiotherapy as the standard of treatment in women with locally advanced cervical cancer.