NIH News Advisory

NATIONAL INSTITUTES OF HEALTH | National Cancer Institute

EMBARGOED FOR RELEASE
Monday, February 22, 1999
10 a.m. EST

NCI Press Office
(301) 496-6641

NCI Issues Clinical Announcement on Cervical Cancer: Chemotherapy Plus Radiation Improves Survival

The National Cancer Institute (NCI) today mailed a clinical announcement to thousands of physicians stating that strong consideration should be given to adding chemotherapy to radiation therapy in the treatment of invasive cervical cancer.

The mailing alerts physicians who treat cancer to the findings of five different studies — all large, randomized clinical trials — showing that women in the studies benefitted from the use of radiation therapy and chemotherapy given together. Up to now, surgery or radiation therapy alone has been considered the standard treatment for cervical cancer that has spread locally (within the cervix) or regionally (within the pelvis).

"The findings of these five trials are remarkably consistent," said NCI Director Richard D. Klausner, M.D. "They are likely to change the standard of care for invasive cervical cancer."

Three of the studies cited in NCI's clinical announcement will appear in the *New England Journal of Medicine*. Because of their potential implications for public health, the articles about these studies were released today, in advance of their publication date, and are accessible on the Journal's Web site at www.nejm.org. The remaining two studies will be published later in 1999.

Several hundred women were enrolled in each of the five trials, which were carried out by NCI's Clinical Trials Cooperative Groups in centers around the country. Their cancers varied from disease confined to the cervix to disease that had spread from the cervix to other pelvic tissues.

In three of the studies, women were randomly divided into groups, or "arms" that received either radiation alone or radiation plus concomitant chemotherapy (given at the same time as the radiation therapy). The chemotherapy agents used were cisplatin and 5-fluorouracil, also known as 5-FU (two studies) and cisplatin alone (one study). In all three trials, the proportion of women alive after about three years of follow-up was higher in the groups receiving chemotherapy plus radiation than in those receiving only radiation therapy.

In the two other studies, all patients received concomitant chemotherapy and radiation. However, the chemotherapy drugs differed between the arms. In one arm of each of these trials, the chemotherapy used was hydroxyurea while in the other arms, the chemotherapy included cisplatin. In both trials, the groups who received cisplatin had better survival rates.

NCI's clinical announcement states that, although the best chemotherapy regimen for cervical cancer has not been determined, "significant results were seen using cisplatin alone or cisplatin in combination with 5-FU and other agents."

NCI's Clinical Announcement is available from the NCI Press Office (301) 496-6641 and on NCI's Web site for clinical trials: http://cancertrials.nci.nih.gov. It can also be obtained from CancerFax; call (301)

402-5874 from a fax machine and use the CancerFax code number for this document, 400262, when prompted.

For more information about cancer visit NCI's Web site for patients, public and the mass media at NCI's main Web site at http://www.nci.nih.gov.

Attachments:
1) Clinical Trials of Concurrent Chemotherapy and Radiation Therapy for Cervical Cancer;
2) Concurrent Chemotherapy and Radiation for Cervical Cancer: Questions and Answers

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Clinical Trials of Concurrent Chemotherapy and Radiation Therapy for Cervical Cancer

GOG 85: A Randomized Comparison of Fluorouracil Plus Cisplatin Versus Hydroxyurea as an Adjunct to Radiation Therapy in Stages IIB-IVA Carcinoma of the Cervix With Negative Para-Aortic Lymph Nodes: A Gynecologic Oncology Group and Southwest Oncology Group Study
Principal Investigator: Charles W. Whitney, M.D., Christiana Hospital, Newark, Del.
Publication: *Journal of Clinical Oncology*, in press.

RTOG 9001: Pelvic Radiation With Concurrent Chemotherapy Versus Pelvic and Para-Aortic Radiation for High-Risk Cervical Cancer: A Randomized Radiation Therapy Oncology Group Clinical Trial
Principal Investigator: Mitchell Morris, M.D., The University of Texas M. D. Anderson Cancer Center, Houston
Publication: *New England Journal of Medicine*, in press.

GOG 120: Concurrent Cisplatin-Based Chemoradiation Improves Progression-Free and Overall Survival in Advanced Cervical Cancer: Results of a Randomized Gynecologic Oncology Group Study
Principal Investigator: Peter Rose, M.D., Case Western Reserve University and University Hospitals of Cleveland
Publication: *New England Journal of Medicine*, in press.

SWOG: Cisplatin and 5-Fluorouracil Plus Radiation Therapy are Superior to Radiation Therapy as Adjunctive Therapy in High-Risk Early-Stage Carcinoma of the Cervix After Radical Hysterectomy and Pelvic Lymphadenectomy: Report of a Phase III Intergroup Study
Principal Investigator: William Peters III, M.D., Puget Sound Oncology Consortium and University of Washington, Seattle
Presentation: Society of Gynecologic Oncologists, March 22, 1999

GOG 123: A Comparison of Weekly Cisplatin During Radiation Therapy Versus Irradiation Alone, Each Followed by Adjuvant Hysterectomy in Bulky Stage IB Cervical Carcinoma: A Randomized Trial of the Gynecologic Oncology Group
Principal Investigator: Henry M. Keys, M.D., Albany Medical College, Albany, N.Y.
Publication: *New England Journal of Medicine*, in press.

Concurrent Chemotherapy and Radiation for Cervical Cancer
Questions and Answers

The National Cancer Institute (NCI) has issued a clinical announcement stating that strong consideration should be given to adding concurrent chemotherapy to radiation therapy in the treatment of invasive cervical cancer. This fact sheet answers questions about the five major studies that led to this recommendation and their implications for patients.

1. Why did NCI issue this clinical announcement?

NCI issued the clinical announcement because new, conclusive information has emerged. The results of five large studies have shown that chemotherapy that includes the drug cisplatin, when given at the same time as radiation therapy, prolongs survival in women with invasive cervical cancer. Up to now, surgery or radiation alone has been considered standard treatment for this form of cancer. The new findings are expected to change the standard of care.

2. What were the five studies?

The studies were carried out by three of NCI's Clinical Trials Cooperative Groups, which are consortiums of institutions and physicians that conduct trials jointly. All were phase III trials — that is, they were studies in which one treatment is compared to another. Each of the trials included several hundred patients. All had invasive cervical cancer, ranging from disease that had spread locally, within the cervix, to disease that had spread regionally, to other parts of the pelvis (stages IA2, IB, II, III, and IVA according to the staging system used by the International Federation of Gynecologic Oncology, or FIGO).

- **Gynecologic Oncology Group (GOG) 85**[1]

  A. Radiation therapy together with the drugs cisplatin and 5-fluorouracil (5-FU) vs.
  B. Radiation therapy with the drug hydroxyurea.
  386 *patients, stages IIB, III, and IVA, enrolled 1986-1990.*
  Results: Three years from the time of diagnosis, 67 percent of women receiving radiation with cisplatin and 5FU were alive compared to 57 percent of those receiving radiation therapy and hydroxyurea.

- **Radiation Therapy Oncology Group (RTOG) 9001**[2]

  A. Radiation therapy with 5-FU and cisplatin vs.
  B. Radiation therapy alone
  389 *patients, stages IIB, III, and IVA, enrolled 1990-1997*
  Results: The three-year survival rate for women receiving cisplatin and 5-FU is 75 percent compared to 63 percent for women receiving radiation alone.

- **Gynecologic Oncology Group (GOG) 120**[3]

  A. Radiation therapy with cisplatin vs.
  B. Radiation therapy with cisplatin, 5-FU, and hydroxyurea versus
  C. Radiation therapy with hydroxyurea.
  526 *patients, stages IIB, III, IVA, enrolled 1992-1997*
  Results: In both groups receiving radiation and cisplatin, the three-year survival rate is 65 percent compared to 47 percent for women receiving radiation and hydroxyurea.

- **Southwest Oncology Group (SWOG) 8797**[4]

  A. Radiation therapy with 5-FU and cisplatin vs.
  B. Radiation therapy alone
  243 *patients, stages IA2, IB, IIA, with adverse pathology found at time of surgery, enrolled 1992-1996*
  Results: The three-year survival rate for women receiving radiation and cisplatin and 5-FU is 87 percent compared to 77 percent for women receiving radiation alone.

- **Gynecologic Oncology Group (GOG) 123**[5]

  A. Radiation therapy with cisplatin vs.
  B. Radiation alone

368 p*atients, stage IB bulky, enrolled 1992-1997*
Results: With half of the patients followed for 35.7 months or more, 83 percent of those who received concurrent chemotherapy and radiation therapy are alive, compared to 74 percent of those treated with radiation therapy alone.

3. How has the combined chemoradiation affected length of survival?

More follow up with the patients is needed before investigators will have complete answers to this question. In four of the five trials, patients were enrolled and treated up until 1996 or 1997, and the majority are still alive. In the trial begun earlier (GOG 85) the majority of patients receiving cisplatin-based chemotherapy with radiation were still alive seven and a half years after diagnosis (89.4 months). In contrast, half of the patients on the other arm of this trial — those who received hydroxyurea and radiation — had died by about five years (59.8 months).

Overall, across the five studies, concurrent cisplatin-based chemoradiation reduced the risk of death by 30 percent to 50 percent.

4. Were any of these trials halted because of the results?

No. The trials were already closed to enrollment and all treatments had been completed before the survival data became available. However, based on these study results, the Gynecologic Oncology Group's Data and Safety Monitoring Committee has voted to close the radiation-only arm of another cervical cancer treatment study (GOG 165).

5. In light of these studies, which cervical cancer patients should consider treatment with concurrent chemotherapy and radiation?

The findings apply to women diagnosed with International Federation of Gynecologists and Obstetricians (FIGO) stages IB-IVA as well as those with stage IA, and IIA who have metastatic disease in the pelvic lymph nodes, positive parametrial disease (cancer cells found in the parametrium, the connective tissue surrounding the uterus), or positive surgical margins (cancer cells found in the tissues surrounding the removed tumor).

6. What chemotherapy drugs were used in these studies?

Three different drugs were used. Cisplatin was used in all of the trials. Hydroxyurea and 5-fluorouracil (5-FU) were used in some of the trials as well.

7. Did the type of chemotherapy make any difference in the outcome of these studies?

Yes, chemotherapy that included cisplatin improved survival. In two of the trials, women in one group received chemotherapy including cisplatin together with radiation while women in the other group received one of the other drugs together with radiation. Those who received the cisplatin/radiation combination had better survival rates.

However, it is not possible from these trials to conclude which cisplatin-based regimen is the optimal one — whether it is cisplatin alone, cisplatin combined with 5-FU, or perhaps some other combination. Further studies will be needed to establish the optimal chemotherapy to accompany radiation therapy.

8. What kinds of radiation therapy were used?

All patients on all arms of these trials received radiation therapy directed at the pelvic area from an external source. In four of the trials, they also received intracavitary radiation, which is supplied by radioactive pellets temporarily placed in the vagina and cervix. None of the trials compared one kind of radiation to another.

9. What were the side effects of chemotherapy and radiation therapy given at the same time? Were they worse than the side effects of radiation alone?

The severe side effects were mainly leukopenia (low number of white blood cells) and nausea and vomiting. These were more frequent and more severe in the women who had the combined therapy than in those who had radiation alone. In general, these adverse effects were temporary and manageable. For instance, women with leukopenia stopped chemotherapy until their blood counts rose and then were able to resume the treatments.

10. Why were chemotherapy and radiation given at the same time, instead of one after another?

Previous, smaller studies have suggested that chemotherapy and radiation therapy are synergistic — together they have a greater effect than would be expected based on their effects when given alone. The reason for this is not clear, but researchers think it may be that chemotherapy makes cells more sensitive to radiation, or vice versa. It is also possible that chemotherapy stops cancer cells from repairing the damage caused by radiation.

11. What other cervical cancer studies are going on or planned at this time?

Treatment studies are comparing different kinds and combinations of chemotherapy. Investigators are also looking at the impact of both surgery and radiation therapy on quality of life and at ways to improve quality of life after treatment.

Other important research focuses on vaccines to treat cervical cancer. Because cervical cancer is linked to a virus — the human papillomavirus or HPV — a vaccine targeted at the virus might be effective in treating the disease. Several different treatment vaccines are under development at centers around the world. At NCI, planning is under way for an Institute-sponsored, multicenter trial to test a vaccine as adjuvant treatment after radiation therapy or surgery.

Several prevention vaccines are also in development. One of these, developed at NCI, has succeeded in stimulating the body to produce antibodies to HPV, according to early data from its first trial in humans. If further follow up and analysis confirm these early findings, the vaccine will be tested in larger numbers of women, including those at risk for development of HPV infection.

Researchers are also looking for ways to manage the mild cervical abnormalities that sometimes progress to cervical cancer. NCI's ASCUS/LSIL Triage Study, or ALTS, is evaluating:

- immediate colposcopy — a procedure in which a physician examines the cervix through a magnifying instrument and biopsies any abnormal areas
- repeating the Pap test every six months (because most abnormalities return to normal without treatment)
- testing for certain types of HPV as a means to differentiate between abnormalities that need immediate colposcopy and those that can be best followed with repeat Pap tests at six-month intervals

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1. Whitney, C.W., et al., *Journal of Clinical Oncology*, in press.

2. Morris, M., et al., *New England Journal of Medicine*, in press; available on the Journal's Web site, www.nejm.org.

3. Rose, P.G., et al., *New England Journal of Medicine*, in press; available on the Journal's Web site, www.nejm.org.

4. Peters, W., et al., to be presented at the annual meeting of the Society of Gynecologic Oncologists, March 22, 1999.

5. Keys, H.M., et al., *New England Journal of Medicine*, in press; available on the Journal's Web Site, www.nejm.org.
