Anti-Cancer Drugs, 4, pp. 335–337

Metastatic adenocarcinoma of the endometrium treated with 13-*cis*-retinoic acid plus interferon-α

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Phase II trials of the novel biologic combination of 13-*cis*-retinoic acid plus interferon (IFN)-α have achieved major activity in advanced squamous cell carcinomas of the skin and cervix, but not of the lung or head and neck. Very limited study of this combination has occurred in cancers other than those of squamous type. Although uncommon, cases of unresectable or metastatic endometrial adenocarcinoma are virtually incurable, and chemotherapy has had no impact on survival in these cases. This report describes our use of 13-*cis*-retinoic acid plus IFN-α to treat a case of cisplatin- and hormone-resistant, locally advanced and distantly metastatic adenocarcinoma of the endometrium. In this worst-prognosis case, the biologic therapy achieved a major response, which persisted for 4 months. Based on the dramatic activity in this case, we believe that depthful mechanistic and clinical study of this promising new biologic combination should be expanded to include non-squamous tumors of many different sites and histopathologic types.

Key words: Adenocarcinoma, 13-cis-retinoic acid, endometrium, interferon-α.

Introduction

Adenocarcinoma of the endometrium is the most common invasive neoplasm of the female genital tract. In the US, 34 000 new cases of this cancer occur annually.[1] In more than 85% of cases, the diagnosis occurs while the adenocarcinoma is localized in the uterus, the only symptom being painless peri- or postmenopausal bleeding. When diagnosed thus, the 5-year survival rate after standard surgery is over 80%. In the minority of primary cases, when this cancer advances to other pelvic sites or metastasizes to distant sites, the 5-year survival rate after surgery with or without radiotherapy is under 10%.[2]

We report here on a patient who presented with locally advanced endometrial adenocarcinoma. Her primary treatment consisted of a partial resection followed by chemotherapy for residual, unresectable, local disease. While still on chemotherapy, the cancer advanced locally and developed distant metastases in the lung. We then treated the patient with the promising new biologic combination of 13-*cis*-retinoic acid and interferon (IFN)-α. This choice of systemic biologic therapy was based on the patient's poor prospects for survival and on the strong activity of 13-*cis*-retinoic acid plus IFN-α in the gynecologic malignancy advanced squamous cell carcinoma of the cervix.[3,4]

Clinical presentation

This 60-year-old patient presented with postmenopausal bleeding. Chest radiograph, contrast barium enema and proctosigmoidoscopy were all negative, indicating non-metastatic primary disease. After a biopsy of involved tissue, diagnosis prior to surgery was endometrial adenocarcinoma.

Primary treatment began with a laparotomy, which revealed a moderate amount of ascitic fluid and diffuse omental adenocarcinoma extending to the hepatic flexure. During the laparotomy, an inspection of the pelvic cavity revealed nodularity posterior to the uterus. Next, the patient underwent a total abdominal hysterectomy, removal of both ovaries and a partial infracolic omentectomy. The posterior aspect of the uterus was adherent to the rectum. An unresectable necrotic tumor mass was present in the cul-de-sac.

The uterine tumor formed a polypoid mass of 4.5 × 2.0 cm. The tumor extended into the upper cervical canal and tumor cells were present in the serosal lymphatics. Histopathologic examination of resected tumor tissue indicated a grade 2 adenocarcinoma with papillary features suggesting a papillary serous carcinoma that involved the omentum and ascitic fluid.

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The ovaries and fallopian tubes were free of cancer.

Seven cycles of systemic therapy of 75 mg/m^2 of single-agent cisplatin every 3–4 weeks were given for the unresectable local disease. The patient's disease had a minor response after four cycles, but progressed locally after seven cycles and developed a lung metastasis. Cisplatin was stopped, and hormonal therapy of tamoxifen (40 mg/day) and medroxyprogesterone acetate (160 mg/day) was started. After 1 month of the new therapy, the patient's disease progressed both locally and in the lung and the hormonal therapy also was stopped.

She now had locally advanced, metastatic endometrial adenocarcinoma resistant to cisplatin and hormonal therapy. Her performance status was still good. We started treatment with oral 13-*cis*-retinoic acid (1 mg/kg/day) and subcutaneous IFN-α (3 MU/day). We also gave her vitamin E (800 IU b.i.d.) to reduce the toxic effects of 13-*cis*-retinoic acid.[5] The patient tolerated the combination therapy well, experiencing only mild dry skin and a transient fever. At 4 weeks of therapy, she experienced a minor response in the lung and pelvis. Permitted by the combination's low toxicity, we increased her IFN-α to 4.5 MU/day. The cancer continued to respond. After 2 months, a partial response occurred in both the pelvis and lung (Figure 1). This partial response lasted 4 months, after which the disease progressed in the pelvis and lung while therapy continued. We then stopped the 13-*cis*-retinoic acid plus IFN-α and started carboplatin. This new therapy was ineffective and the cancer continued to progress.

Discussion

The case of endometrial adenocarcinoma we report here is one of very few instances when combined 13-*cis*-retinoic acid and IFN-α was used to treat other than squamous cell carcinoma.[6] We are not

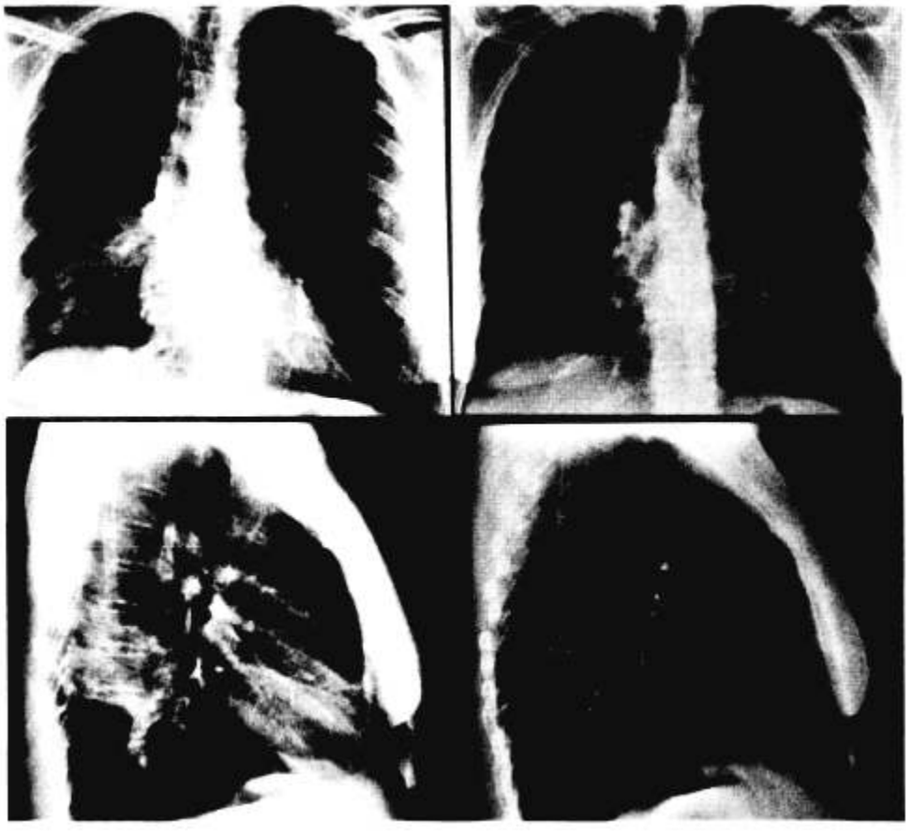

Figure 1. Left top and bottom panels: pretreatment PA and lateral chest radiographs showing a large right lower lobe parahilar metastasis. Right top and bottom panels: a partial response was observed following 3 months treatment with 13-*cis*-retinoic acid plus IFN-α.

aware of any other report of the use of this combination to treat adenocarcinoma. This novel biologic regimen only recently entered phase II clinical trials, most of which were or are in squamous cell carcinoma of various sites. The combination has not achieved any major activity in trials involving squamous cell carcinoma of the lung or head and neck.[7,8] It has achieved major activity in advanced squamous cell carcinoma of the skin (including cases of regional or distant metastases)[9] and in locally advanced squamous cell carcinoma of the cervix (including cases of very bulky tumors—10 cm or greater in at least one dimension).[3,4]

Many positive characteristics of this combination support its clinical study.[3,4,9,14] Previous data demonstrate that these two agents have different mechanisms of action and non-overlapping toxic effects. *In vitro* synergistic and additive effects of combined all-*trans*-retinoic acid (a close relative of 13-*cis*-retinoic acid) and IFN-α have been observed in many human cell lines, including three of breast adenocarcinoma.

Although we report only one case, it is a highly unusual and suggestive case. After progressing first on cisplatin and then on hormonal therapy, our patient's locally advanced and metastatic endometrial adenocarcinoma had a major response in local and distant sites to 13-*cis*-retinoic acid plus IFN-α. This suggests the possibility that this biologic combination can add to other chemotherapeutic approaches for helping currently virtually incurable cases of this cancer.

Trials of hormonal therapies in advanced or recurrent endometrial carcinoma with no prior systemic therapy have achieved response rates of 15–25%. In the same disease setting, trials of the cytotoxic agents cisplatin, carboplatin, doxorubicin, cyclophosphamide and ifosfamide have achieved response rates of 15–30%.[2] After failing initial chemotherapy, endometrial adenocarcinoma's response rate to subsequent cytotoxic or hormonal therapy is under 10%. A high priority has been placed on developing new approaches, such as combined 13-*cis*-retinoic acid and IFN-α, for treating recurrent, advanced or metastatic endometrial adenocarcinoma.

The armamentarium we have for treating this and other refractory solid tumors is quite limited. Although combined 13-*cis*-retinoic acid and IFN-α has been studied almost exclusively in squamous cell carcinoma of various sites, this case of dramatic activity in cisplatin-resistant metastatic endometrial adenocarcinoma suggests that mechanistic and clinical study of this combination should be expanded to solid tumors of many different sites and histopathologic types. This active, well-tolerated biologic regimen may provide valuable new options for multimodality treatment of refractory solid tumors.[3,4,9–16]

References

1. Boring CC, Squires TS, Tong T. Cancer Statistics, 1993. *CA Cancer J Clin* 1993; **43**: 7–26.
2. Park RC, Grigsby PW, Muss HB, Norris HJ: Corpus: epithelial tumors. In: Hoskins WK, Perez CA, Young RC, eds. *Principles and practice of gynecologic oncology*. Philadelphia: JB Lippincott 1992; 663–93.
3. Lippman SM, Kavanagh JJ, Paredes-Espinoza M, *et al.* 13-*cis*-retinoic acid plus interferon alpha 2a: highly active systemic therapy for squamous cell carcinoma of the cervix. *J Natl Cancer Inst* 1992; **84**: 241–5.
4. Lippman SM, Kavanah JJ, Paredes-Espinoza M, *et al.* 13-*cis*-retinoic acid plus interferon-α2a in locally advanced squamous cell carcinoma of the cervix. *J Natl Cancer Inst* 1993; **85**: 499–500.
5. Besa EC, Abrahm JL, Bartholomew MJ, *et al.* Treatment with 13-*cis*-retinoic acid in transfusion-dependent patients with myelodysplastic syndrome and decreased toxicity with addition of alpha-tocopherol. *Am J Med* 1990; **89**: 739–47.
6. Dhingra K, Papadopoulos N, Lippman SM, *et al.* Phase II study of alpha-interferon and 13-*cis*-retinoic acid in metastatic melanoma. *Invest New Drugs*; in press.
7. Voravud N, Lippman SM, Weber RS, *et al.* Phase-II study of 13-*cis*-retinoic acid plus interferon-α in recurrent head and neck cancer. *Invest New Drugs*; in press.
8. Rinaldi DA, Lippman SM, Burris HA, *et al.* Phase II study of 13-*cis*-retinoic and interferon-α2a in patients with advanced squamous cell lung cancer. *Anti-Cancer Drugs*; **4**: 33–6.
9. Lippman SM, Parkinson DR, Itri LM, *et al.* 13-*cis*-retinoic acid and interferon α-2a: effective combination therapy for advanced squamous cell carcinoma of the skin. *J Natl Cancer Inst* 1992; **84**: 235–41.
10. Lippman SM, Kessler JF, Meyskens FL Jr. Retinoids as preventive and therapeutic anticancer agents. *Cancer Treat Rep* 1987; **71**: 391–405, 493–515.
11. Smith MA, Parkinson DR, Cheson BD, *et al.* Retinoids in cancer therapy. *J Clin Oncol* 1992; **10**: 839–64.
12. Borden EC. Interferons expanding therapeutic roles. *N Engl J Med* 1992; **326**: 1491–3.
13. Bollag W, Holdener EE. Retinoids in cancer prevention and therapy. *Ann Oncol* 1992; **3**: 513–26.
14. Marth C, Kirchebner P, Daxenbichler G. The role of polyamines in interferon and retinoic acid mediated synergistic antiproliferative action. *Cancer Lett* 1989; **44**: 55–9.
15. Chang AY, Keng PC. Potentiation of radiation cytotoxicity by recombinant interferons, a phenomenon associated with increased blockage at the G_2–M phase of the cell cycle. *Cancer Res* 1987; **47**: 4338–41.
16. Rutz HP, Little JB. Modification of radiosensitivity and recovery from X ray damage *in vitro* by retinoic acid. *Int J Radiat Oncol Biol Phys* 1989; **16**: 1285–8.

(Received 16 February 1993; accepted 18 March 1993)