Pelvic relapses in ovarian cancer. Role of CA-125, transvaginal ultrasound and color Doppler

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Summary

From January 1995 to January 2001, 40 patients with epithelial ovarian cancer were treated at our Institution. Fourteen of these, with a clinical CR after surgery and platinum-based chemotherapy, were evaluated monthly by gynecological examination, Ca-125 RIA assay, pelvic ultrasound with transabdominal and transvaginal probe and color Doppler.

Six pelvic relapses, from 1.5 to 3.0 cm, were detected by transvaginal ultrasound (US). They showed a rich neovascularization with low resistance, high flow, PI from 0.3 to 1.0 and RI < 0.5 in all cases. US did not reveal any sign of relapse in the remaining eight patients.

In all cases of pelvic relapses ultrasonic signs of recurrence preceded the increase of Ca-125 by one to six months (average 3.8).

Key words: Ovarian Cancer; Pelvic relapse; Ca-125; Transvaginal ultrasound.

Introduction

Follow-up is very important for patients treated surgically and/or with chemotherapy for epithelial ovarian cancer. It can allow for a timely treatment and subsequently increased lifetime. Relapse in these patients is often abdominopelvic.

CA-125 is the most useful tumoral marker in the follow-up of these patients. It picks up the first sign of relapse in 60-70% of cases [1-3]. It has been shown that an increase in serum values can anticipate a clinical or instrumental detection of relapse even by several months [1, 4].

The importance of this tumoral antigen is also further confirmed by the increase of survival rate in patients who have been administered vaccines with ACA 125, a murine monoclonal immunoglobuline anti-idiotype Ab 2 and designated ACA 125 , which mimics a specific epitope on the tumor associated antigen CA-125 [5].

Recent experimental studies also suggest the role of UPA (Urokinase-type Plasminogen Activator) and its inhibitor PAI 1(Plasminogen Activator Inhibitor) in the progression of ovarian cancer [6].

The goal of our study was to compare the use of CA-125, transvaginal ultrasound and color Doppler in the diagnosis of pelvic cancer relapse.

Materials and Methods

From January 1995 to January 2001, we observed 40 patients with epithelial ovarian cancer. After surgery all patients underwent platinum-based chemotherapy. At the end of the chemotherapy cycle, 14 of these patients demonstrated a complete clinical response to the therapy, as proved by the results of clinical examination, level of CA-125, pelvic transabdominal and transvaginal ultrasound and CAT scan with peritoneography. All patients showed CA-125 values > 35 UI/ml at the time of the diagnosis and in all cases these levels were negative at the end of chemotherapy.

The 14 patients with complete response to therapy constitute the subject of our study. During the follow-up, the patients were evaluated monthly with gynecological exams, testing of CA-125 serum levels, pelvic ultrasound with abdominal and transvaginal probe and color Doppler.

Pelvic ultrasound was performed with a transabdominal probe at 3.5 MHz and transvaginal probe at 6.5 MHz using Ansaldo 570. The serum levels of CA-125 were taken through radioimmunoassay (RIA).

Results

All the patients respected the prescribed follow-up program. Six pelvic cancer relapses were detected by transvaginal ultrasound. The dimension of the tumors varied from 1.5 to 3.0 cm. Of these six relapses, four were localized centrally and two in the iliac fossa. In five of the cases, only a single mass was found; while in one case, two masses were present. The common ultrasound markers were non-homogeneous and hypoecogenic tumor with imperfect borders. Color Doppler showed they had a rich neovascularization. The neovascularization observed was characterized by a low resistance and a high flow with a PI that varied from 0.3 to 1.0. The RI resulted lower than 0.5 in all cases. Ascites were not found in any of the patients. The remaining eight cases have not shown signs of pelvic cancer recurrence. In all cases of pelvic relapses ultrasonic signs of relapsing preceded the increase of CA-125 serum levels by one to six months (with an average of 3.8 months).

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Discussion

Around 50% of patients with ovarian cancer with complete response after adjuvant chemotherapy are destined to relapse. CA-125 measurement is the most widely used method in the follow-up of these patients. An increase of CA-125 levels constitutes a sure sign of relapse in more than 90% of cases.

Nevertheless, there is no data that supports the use of CA-125 as the only indicator of relapse in ovarian carcinoma. Therefore, a unanimous consensus in advising its use in follow-up does not exist. Furthermore, not all authors agree about giving second-line chemotherapy to those patients whose CA-125 level is > 35 UI/ml without other signs of relapse [1, 13], but other markers are still experimental and do not have a well defined contribution to make at present .

Transvaginal ultrasound examination, due to its technical characteristics, is a reliable method in the evaluation of pelvic pathologies. Furthermore, ultrasound used along with the color Doppler consents the study of pelvic tumors not only for its ultrasonic criteria but also for its neovascularization. Such data allow a differential diagnosis regarding referable scar tissue due to previous extensive surgery.

In our experience, we have noticed pelvic relapse in ovarian carcinoma using transvaginal ultrasound and color Doppler earlier than we would have with CA-125. Such evidence confirms the hypothesis of Folkman [14, 15] who sustains that a rapidly growing tumor produces its own hematic vessels, which in the past was defined as "tumoral blush".

In our study, these vessels were characterized by a low resistance and a high flow, as confirmed by the international literature [12]. These resources suggest two important clinical implications: first, they show that transvaginal ultrasonography can be integrated with other follow up procedures to overcome the limitations of CA-125 level measurements [11, 16].

Secondly, pelvic ultrasound can diagnose pelvic relapse in ovarian carcinoma earlier.

A new non-invasive diagnostic procedure is immunoscintigraphy. Its diagnostic accuracy, positive predictive value and negative predictive value are 87%, 84% and 100%, respectively. It promises to reliably identify patients who do not require surgical re-exploration and guide biopsies when necessary [17].

The question of the usefulness of an earlier diagnosis of pelvic relapse is still open since its impact must still be defined in terms of survival, response at salvage chemotherapy and consequently the patient's quality of life [18].

References

[1] Porsbjerg C.M., Sorensen J.B.: "The role of tumor marker CA-125 in the treatment of ovarian cancer". *Ugeskr. Laeger.,* 1998, *160* (7), 995.

[2] Gard G.B., Houghton R.S.: "An assessment of the value serum CA-125 measurements in the management of epithelial ovarian carcinoma". *Gynecol. Oncol.,* 1994, *53* (2), 83.

[3] Van der Burg M.E.: "The role of CA-125 in the earlier diagnosis of progressive disease in ovarian cancer". *Ann. Oncol.,* 1990, *1,* 301.

[4] Oehler M.K., Sutterlin M., Caffier H.: "CASA and CA-125 in diagnosis and follow-up of advanced ovarian cancer". *Anticancer Res.,* 1999, *19* (suppl.), 2513.

[5] Wagner U., Kohler S.: "Immunological consolidation of ovarian carcinoma recurrences with monoclonal anti-idiotype antibody ACA 125: immune response and survival in palliative treatment". *Clin. Cancer Res.,* 2001, *7* (5), 1154.

[6] Konecny G., Untch M.: "Association of Urokinase - type plasminogenactivator and its inhibitor with disease progression and prognosis in ovarian cancer". *Clin. Cancer Res.,* 2001, *7* (6), 1743.

[7] Guerriero S., Ajossa S., Risalvato A., Lai M.P., Mais V., Angiolucci M., Melis G.B.: "Diagnosis of adnexal malignancies by using color Doppler energy imaging as a secondary test in persistent masses". *Ultrasound Obstet. Gynecol.,* 1998, *4*, 277.

[8] Alcazar J.L., Errasti T., Zornoza A., Minguez J.A., Galan M.J.: "Transvaginal color Doppler ultrasonography and CA-125 in suspicious adnexal masses". *Int. J. Gynecol. Obstet.,* 1999, *66* (3), 255.

[9] Schneider V.L., Reed A.K.L, Hatch K.D.: "Comparison of Doppler with two dimensional sonography and CA-125 for prediction of malignancy of pelvic masses". *Obstet. Gynecol.,* 1993 (81), 983.

[10] Bromely, Goodman H., Benacerraf B.R.: "Comparison between sonographic morphology and Doppler waveform for the diagnosis of ovarian malignancy". Obstet. Gynecol., 1994 (83), 434.

[11] Laframboise S., Nedelw R.: "Use of CA-125 and ultrasound in high risk women". *Int. J. Gynecol. Cancer,* 2002, *12* (1), 86.

[12] Wan X., Suy: "Color Doppler ultrasound and quantitative histologic study of angiogenesis in ovarian tumor". *Zhonghua Yi Xue Za Zhi,* 2000, *80* (9), 672.

[13] Allen D.J., Baak J., Belpomme D., Berek J.S., Bertelse K., Ten Bokkel H. *et al.*: "Advanced epithelial ovarian cancer, 1993 consensus Statements". *Ann. Oncol.,* 1993 (suppl.), *4,* 83.

[14] Folkman J., Ingber D.: "Inhibition of angiogenesis". *Semin. Cancer Biol.,* 1992 (3), 89.

[15] Folkman J.: "Angiogenesis research: from laboratory to clinic". *Forum* (Genova) 1999, *9* (suppl.) 3, 59.

[16] Maggino T., Gadducci A.: "Serum markers as prognostic factor in epithelial ovarian cancer: an overview". *Eur. J. Gynaecol. Oncol.,* 2000, *21* (1), 64.

[17] Magiani F., Fazio F.: "Diagnosis of persistent ovarian carcinoma with three step immunoscintigraphy". *Br. J. Cancer,* 2000, *82* (3), 616.

[18] Markmann M.: "Resetting CA-125 range for a complete response to chemotherapy, why?". *Gynecol. Oncol.,* 1994 (53), 281.

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