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The role of chemotherapy including ifosfamide for ovarian carcinoma

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Summary. On the basis of the results of earlier studies, 30 departments of gynecology have been cooperating nationwide in Austria since 1980 to promote the use of adjuvant chemotherapy after surgery for cure of ovarian carcinoma in early stages and the role of lymph node dissection and of second-look operation. Results recorded in more than 160 patients treated with adjuvant chemotherapy after so-called radical surgery performed in disease stages I and II demonstrate that only highly differentiated tumours in stage Ia can be cured by surgery only with no further adjuvant treatment. This underlines the necessity for staging. More than 200 patients with TNM stages III and IV were randomized after debulking surgery to receive treatment with different kinds of drug combinations to compare the therapeutic efficacy of a sequential alternating drug regimen consisting of Adriamycin-cisplatin + vincristine-cyclophosphamide + high-dose methotrexate with that of the combination of Adriamycin-cyclophosphamide and that of Adriamycin-cisplatin. High-dosed ifosfamide was also used in pilot studies.

Introduction

Today more women die of ovarian carcinoma than of cervical carcinoma, which has a much higher incidence rate. Reported survival rates of small numbers of patients with malignant ovarian tumors vary extremely widely, which is due more to different selection criteria and different prognostic factors in the patients themselves rather than to variations in therapeutic effectiveness of the different treatment regimens applied. Even the survival of patients with the same tumor stages is influenced by various parameters. In a meta-analysis of 38 articles dealing with a total of 66 treatment groups and 3443 patients, it was found that the main prognostic factors predicting improved survival of patients measured with the log (relative risk) (LRR) are: chemotherapy including cisplatin as initial treatment, a residual tumor mass less than 2 cm^3 in diameter prior to therapy, FIGO stage II/III, and a good performance status. In a multivariate model, the use of cisplatin and the residual tumor were found to be the only factors of prognostic relevance. There was no demonstrable relation between median survival and the overall clinical response rate of all patients. Patients with undifferentiated tumors and patients treated with cisplatin regimens had higher response rates to treatment, but younger patients and those with endometrioid histology were less likely to respond. Surgical complete remission was encountered more frequently in studies that included a high number of patients with small tumor masses prior to treatment. Trials using cisplatin included more patients with small tumor nodules in their patient material than studies not using this drug. The data illustrate the danger of comparing studies with each other. In the trials with high percentages of patients with small tumor residuals in the study population more toxic deaths were seen. This probably reflects the fact that they had received more intensive treatment. The LRR correlated closely with the median survival, response and the percentage of surgical complete remissions [20].

It has long been known that the stage of disease at presentation is an important prognostic feature in ovarian cancer. More recently, however, it has been appreciated that the volume of residual disease is also significant for the prognosis and under certain circumstances can actually be more important than the FIGO stage [9]. In addition, findings have been reported showing that regardless of treatment, progression-free interval and survival are significantly dependent on residual disease category and grade of differentiation [8].

Decisions on and evaluations of the many forms of treatment available are particularly difficult for relatively

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small gynecological departments. For this reason, we began a cooperative, randomized study in 1980, with 30 Austrian departments of gynecology taking part, to evaluate various forms of therapy with reference to stage of disease. It seemed especially important that the prognostic parameters relevant for survival should be evenly distributed over the different therapy groups, so that the results would not be falsified by an incidental accumulation of poor prognostic factors (e.g., large residual tumour mass, low differentiated tumor, etc.) [12]. This study includes 135 patients operated on for cure of stage I or II ovarian cancer, 25 of whom (those with stage Ia of highly differentiated tumors without rupture of the capsule) received no further therapy after primary surgery. A group of 24 patients with stage Ia, poorly differentiated, tumors received whole-abdomen irradiation therapy, and a control group of 20 patients received no further radiotherapy after surgery. Patients with stages Ib, IIa, IIb have been randomized to a group ($n = 27$) with irradiation alone and a group ($n = 24$) receiving two cycles of Adriamycin/cyclophosphamide (A/C) followed by irradiation and a further four cycles of A/C. Those with stages Ic and IIc have been randomized to receive two cycles of Adriamycin/cisplatin (A/P) followed by irradiation and then a further four A/P cycles ($n = 7$) or two cycles of A/C followed by irradiation and then a further four cycles of A/C ($n = 8$).

It was concluded that only Ia, highly differentiated, tumors seem to need no further therapy, providing an exact staging laparotomy has been performed with hysterectomy, bilateral salpingoophorectomy, appendectomy, omentectomy, lymph node resection and peritoneal lavage. Combined polychemotherapy and radiotherapy is superior to irradiation alone. Stages Ic and IIc should be treated with aggressive polychemotherapy, as recommended for stage III and IV ovarian cancer patients [16].

The presence of steroid hormone receptors in epithelial ovarian cancers has been known for some time, but their clinical significance is still uncertain. Recent data suggest that the ovary is not only the principal source of estrogens and progestins, but also a target organ for these hormones. About 24% of patients with inoperable ovarian carcinoma were reported to respond to endocrine therapy. Therefore we also determined estrogen (ER) and gestagen receptors (PgR) in our studies, the aim being to find in a fairly large number of patients whether ovarian carcinoma contains ER and PgR in sufficient amounts to justify the consideration of adjuvant endocrine therapy. It is important that the treatments available be improved upon, since a secondary spread of ovarian carcinoma is observed in 75% of patients when the primary disease is diagnosed. In addition, patients who are ER- and PgR-positive should benefit from hormone therapy even if chemotherapy is not possible. A study on the determination of hormone receptors in ovarian carcinoma seems justified, since this topic has not been well documented. The present data combine to suggest that receptor assays should become a useful tool in the management of patients with ovarian carcinomas. In addition, ER and PgR determinations provide a prognostic index and may improve the possibility of predicting which well-differentiated stage I ovarian carcinomas are likely to recur [18]. A heterogeneous distribution of the steroid hormone receptors became evident on analysis of several tissues samples from different parts of the tumors [15].

As expected, more patients in stages III and IV have entered our trials than patients in stages I and II. Patients with ovarian cancer stage III and IV have been randomized to two treatment groups to compare a standard chemotherapy with a newly designed "changing scheme" according to which an alternating sequence of three different drug combinations is administered [4, 5].

The prognostic factors were stratified by means of specific computer-assisted randomization. The changing scheme seems to be superior for the subgroups of patients with highly differentiated tumors, without ascites, with larger postoperative tumor burden and with liver metastases. This form of therapy is as effective for women with advanced ovarian cancer, but has much lower toxicity, because of the less frequent cisplatin administrations, than the standard Adriamycin-cisplatin combination [13, 14].

Our findings concerning the second-look laparotomy performed in 151 patients with stage III and IV epithelial ovarian carcinoma who had responded to primary surgery and chemotherapy were important. Among 79 patients who appeared clinically to be free of disease, 19% had microscopic recurrences and 23% had macroscopic residual disease at a second-look operation. The 5-year survival rate for patients with no histological and for those with microscopic secondaries at second-look operation were 55% and 35%, respectively. Only patients with well- or moderately well-differentiated tumors and a small residual tumor mass at first operation had a good prognosis after a second-look operation even without further chemotherapy. Median survival after secondary debulking was 15–17 months and was independent of the radicality of the second-look procedure. Outside of clinical trials second-look laparotomy should therefore only be performed as a diagnostic procedure in patients with well-differentiated or moderately well-differentiated tumors who are left with a small residual tumor mass after the first operation, because in this group of patients chemotherapy can be discontinued after a negative second-look operation [17]. This is in agreement with other findings [10, 11, 21].

The survival of patients with ovarian germ cell malignancies has improved markedly with the administration of chemotherapy after tumor debulking. Nonetheless, there is still a significant number of patients in whom the tumors will progress or recur despite the administration of primary chemotherapy. In the treatment of most solid tumors, including ovarian cancers, the administration of second- or third-line chemotherapy after failure of initial agents usually results in the development of severe toxicity in the face of continued tumor growth. No regimen has yet been devised that is consistently effective for the treatment of patients with disease that is refractory to primary therapy [6]. Future improvement in results depends on current investigations of noninvasive methods for diagnosis and evaluation, better definition of the value of greater dose intensity and alternative routes of administration, the value

of selection methods for appropriate drugs, and the development of new agents and of methods of overcoming drug resistance [7, 19].

From the viewpoint of pharmacology, it appeared earlier that with cyclophosphamide a certain optimum status had been reached; however, it has since emerged that ifosfamide is a cytostatic with remarkable chemotherapeutic properties of its own. The small differences in the chemical structure alter the metabolism in vivo and result in distinct changes in the pharmacokinetics and pharmacodynamics [3]. Antitumor activity was greater for ifosfamide (IFO) than for cyclophosphamide (CYC) in several experimental tumors, some of which were primarily resistant to CYC. The few comparative controlled clinical trials reported suggest superior single-agent activity for IFO than for CYC in soft tissue sarcoma [2] and ovarian cancer [1, 22]. In pilot studies in patients with advanced ovarian cancers we have seen impressive tumor regressions after i.v. administration of IFO, and we therefore plan to continue the use of IFO.

References

1. Brade W, Seeber S, Herdrich K (1986) Comparative activity of ifosfamide and cyclophosphamide. Cancer Chemother Pharmacol 18 [Suppl 2]: S1–S9
2. Bramwell VHC, Mouridsen HT, Santoro A, Blackledge G, Somers R, Verwey J, Dombernowsky P, Onsrud M, Thomas D, Sylvester R, Van Oosterom A (1987) Cyclophosphamide versus ifosfamide: final report of a randomized phase II trial in adult soft tissue sarcomas. Eur J Cancer Clin Oncol 23: 311–321
3. Brock N (1989) Oxazaphosphorine cytostatics: past-present-future. Cancer Res 49: 1–7
4. Dittrich C, Salzer H, Sevelda P, Gitsch E, Karrer K, Rainer H, Moser K, and Austrian Collaborative Ovarian Cancer Study Group (1985) Prospective randomized trial in ovarian cancer of stages III and IV: changing scheme (Adriamycin/cistatin – vincristine/cyclophosphamide – high-dose methotrexate) versus A/P (Adriamycin/cisplatin) versus A/C (Adriamycin/cyclophosphamide). In: Recent advances in chemotherapy – anticancer section. University of Tokyo Press, Tokyo
5. Gitsch E, Salzer H, Schönbauer M, Langer M, Smekal G, Karrer K, Moser K, Rainer H, Dittrich C, Schemper M, and Austrian Collaborative Study Group for the Treatment of Ovarian Cancer (1983) Preliminary results of a randomized cooperative trial in Austria. Five-drug sequential therapy versus standard chemotherapy in ovarian cancer stage III and IV. Proceedings of the 13th International Congress of Chemotherapy, Vienna, 28. 8. 1983 to 2. 9. 1983
6. Howell SB, Zimm S, Markman M, Abramson IS, Cleary S, Lucas WE, Weiss RJ (1987) Long-term survival of advanced refractory ovarian carcinoma patients with small-volume disease treated with intraperitoneal chemotherapy. J Clin Oncol 5: 1607–1612
7. Mulder POM, Willemse PHB, Aalders JG, De Vries EGE, Sleijfer DT, Smit Sibinga TC, Mulder NH (1989) High-dose chemotherapy with autologous bone marrow transplantation in patients with refractory ovarian cancer. Eur J Cancer Clin Oncol 25: 645
8. Omura GA, Bundy BN, Berek JS, Curry H, Delgado G, Mortel R (1989) Randomized trial of cyclophosphamide plus cisplation with or without doxorubicin in ovarian carcinoma: a Gynecologic Oncology Group study. J Clin Oncol 7: 457–465
9. Ozols RF, Young RC (1984) Chemotherapy of ovarian cancer. Semin Oncol 11: 251–263
10. Podratz KC, Malkasian GD, Hilton JF, Harris EA, Gaffey TA (1985) Second-look laparotomy in ovarian cancer: evaluation of pathologic variables. Am J Obstet Gynecol 8: 152–230
11. Rubin SC, Hoskins WJ, Hakes TB, Markman M, Reichman BS, Chapman D, Lewis JL (1989) Serum Ca 125 levels and surgical findings in patients undergoing secondary operations for epithelial ovarian cancer. Am J Obstet Gynecol 160: 667–671
12. Salzer H, Gitsch E, Schönbauer M, Langer M, Smekal G, Karrer K, Moser K, Rainer H, Dittrich C, Schemper M (1983) Cooperative treatment of ovarian cancer stage I–IV. Preliminary results in 226 patients randomized nationwide. Proceedings of the 13th International Congress of Chemotherapy, Vienna, 28. 8. 1983 to 2. 9. 1983
13. Salzer H, Gitsch E, Dittrich C, Sevelda P, Karrer K, Schemper M, Stempel-Smekal G, Langer M, Wagner G, Rainer H, Moser K, Czerwenka K, Breitenecker G, Spona J, und Österreichische Arbeitsgemeinschaft zur Therapie des Ovarialkarzinoms (1985) Ergebnisse der ersten multizentrischen österreichischen Ovarialkarzinomstudie: Prospektiv randomisierter Vergleich einer sequentiellen Chemotherapie (Adriamycin/Cisplatin-Vincristin/Cyclophosphamid-Methotrexat) mit 2 Standard-Schemata (Adriamycin/Cyclophosphamid oder Adriamycin/Cisplatin) bei Patientinnen der Stadien III and IV. Geburtsh Frauenheilkd 45: 761–768
14. Salzer H, Dittrich C, Sevelda P, Gitsch E, Karrer K, Rainer H, Moser K and Austrian Collaborative Ovarian Cancer Study Group (1986) Prospective randomized trial in ovarian cancer of the stages III and IV: changing-scheme versus A/P versus A/C. In: Abstracts of lectures, symposia and free communications of the 14th International Cancer Congress, Budapest, 21–27. 8. 1986 vol 3
15. Schieder K, Kölbl H, Bieglmayer C, Breitenecker G (1987) Heterogene Verteilung von Steroidhormonrezeptoren bei Ovarial- und Endometriummalignomen. Tumor Diagn Ther 8: 171–176
16. Sevelda P, Salzer H, Dittrich C, Moser K, Karrer K, Gitsch E (1986) A prospective randomized study of ovarian patients stage I and II: radiation therapy versus chemotherapy-radiation combined modality treatment. in: Abstracts of lectures, symposia and free communications of the 14th International Cancer Congress, Budapest, 21–27. 8. 1986, Budapest, vol 3
17. Sevelda P, Dittrich C, Salzer H (1989) The value of second-look operation in patients with advanced epithelial ovarian carcinoma. Arch Gynecol Obstet 244: 79–86
18. Spona J, Gitsch E, Salzer H,, Karrer K, and Collaborative Study Group (1983) Estrogen and gestagen receptors in ovarian carcinoma. Gynecol Obstet Invest 16: 189–198
19. Thipgen JT, Vance RB, Lambuth BW (1988) Ovarian carcinoma: the role of chemotherapy. Semin Oncol 15 [Suppl 3]: 16–23
20. Voest EE, Van Houwelingen JC, Neijt JP (1989) A meta-analysis of prognostic factors in advanced ovarian cancer with median survival and overall survival [measured with the log (relative risk)] as main objectives. Eur J Cancer Clin Oncol 25: 711
21. Wiltshaw E, Raju KS, Dawson J and The Ovarian Tumor Group, Royal Marsden Hospital, London (1985) The role of cytoreductive surgery in advanced carcinoma of the ovary: an analysis of primary and second surgery. Br J Obstet Gynecol 92: 522 CC, 28/25, 234
22. Zalupski M, Baker LH (1988) Ifosfamaide. JNCI 80: 556–566