Long-Term Results of Immunochemotherapy for Advanced Ovarian Cancer

HARUO NISHIMURA, KINYA HAMAGUCHI, SHIGEAKI IWANAGA, NOBUMASA TATENO, HIDEAKI AKIZUKI, HIROSHI IDE AND MICHIAKI YAKUSHIJI

Department of Obstetrics and Gynecology, Kurume University School of Medicine, Kurume, 830 Japan

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Summary: Fifty-one patients with stage III and IV ovarian adenocarcinoma underwent initial cytoreductive surgery at Kurume University Hospital between January 1982 and October 1985. They were assigned postoperatively by randomized trials to immunochemotherapy or chemotherapy alone. Of all 51 patients, long-term results of immunochemotherapy for 43 patients were evaluated versus radicality of initial cytoreductive surgery. As a result, the group of patients treated with immunochemotherapy tended to have a better prognosis than the group of patients treated with chemotherapy alone, whereas no statistical difference was observed between the two groups. Moreover, no significant difference was observed in the monitoring of OKT 4/8 ratio between the two groups. However, immunochemotherapy produced a favorable prognosis in the patients with residual disease of greater than 2cm in diameter at initial surgery. In conclusion, these data suggested that immunochemotherapy may have some impact on survival of patients with ovarian adenocarcinoma.

Key words: immunochemotherapy—ovarian cancer—adenocarcinoma—long-term survival—OKT 4/8

Introduction

Chemotherapeutic agents used in cancer treatment are known, with a few exceptions, to have immunosuppressive effects, and this was found also in our previous study of induction chemotherapy in which several drugs including cisplatin (CDDP) were used (Hamai et al. 1984). The immunological abilities of cancer-bearing patients are already reduced, and the degree of this reduction is greater as the cancer is more advanced (Hamai et al. 1985). The use of chemotherapeutic agents that induce further immunosuppression includes extremely poor conditions in cancer patients and exposes them to an immunological disadvantage. This has led to the the concept of immunochemotherapy, which is designed to restore the reduced immunological abilities of cancer-bearing patients as well as to enhance the anticancer effects of chemotherapy by preventing the associated immunosuppression.

Since January, 1982, we have assigned patients with stage III and IV ovarian adenocarcinoma to immunochemotherapy using OK-432 by means of the envelope method. In this study, the usefulness of immunochemotherapy was assessed by evaluating the long-term results according to the degree of completion of surgery in the subjects confined to patients with stage III or IV adenocarcinoma with a minimum of 5 years' follow-up after
the treatment.

Subjects and Methods

Fifty-one patients with stage III and IV ovarian adenocarcinoma underwent initial operation at the Department of Obstetrics and Gynecology, Kurume University School of Medicine between January, 1982 and October, 1985 and were assigned to immunochemotherapy or chemotherapy alone by the envelope method. Forty-three patients who underwent 3 or more courses of induction chemotherapy after initial operation and were followed-up for at least 5 years were evaluated.

Chemotherapy consisted of 3 or more courses. Immunochemotherapy was carried out, in principle, by subcutaneous administration of 3 KE of OK-432 every other day during 7 days before the initiation of chemotherapy, and 5 KE at 2-week intervals for at least 6 months after discharge (Fig. 1).

The analysis was based on comparisons of outcome curves between the two groups, comparisons of survival curves separately for patients with residual tumors of 2 cm or larger at the initial operation and those with less than 2 cm residuals, and changes in the OKT4/8 ratio as the immunological parameter. The characteristics of the two groups was evaluated statistically by means of $\chi^2$ test and t test; the survival; curves were obtained by means of the Kaplan-Meier method, and the differences between the survival curves were examined by means of generalized-Wilcoxon test.

Results

1) Comparisons of patient characteristics

Of the 43 patients evaluated, 22 were assigned to immunochemotherapy, and 21 to chemotherapy alone.

The differences between the two groups in the histopathologic type, clinical stage, performance status (PS), diameter of the residual tumor at the initial operation, type of chemotherapy, and application of a second look operation (SLO) were statistically evaluated by $\chi^2$ test, and those in the mean age by t test. No statistical significance was observed with respect to any of these factors.

2) Comparisons of survival curves in all patients

Five patients of the immunochemotherapy group but only 2 of the chemotherapy group survived for 5 years or longer. The survival curve also tended

![Fig. 1. Immunochemotherapy schedule with OK-432 (Kurume Univ.)](image-url)
to be better in the former group (Fig. 2), but the difference was not statistically significant ($p = 0.05938$).

3) Comparisons of survival curves according to the size of residual tumors at initial operation

The survival curves were compared between the two groups by dividing the patients into those in whom the residual tumors were 2 cm or larger in diameter and those in whom they were less than 2 cm in diameter at initial operation.

The residual tumor was 2 cm or less in diameter in 11 patients of the immunochemotherapy group and 8 patients of the chemotherapy group. No significant differences were observed in their survival curves.

The residual tumor was greater than 2 cm in diameter in 11 patients of the immunochemotherapy group and 13 patients of the chemotherapy group. In the former group, one patient with stage IV endometrioid adenocarcinoma survived for more than 5 years, but none of the latter group survived even for 2 years. The survival curve was significantly better in the case of the immunochemotherapy group than in that of the chemotherapy group (Fig. 4).

4) Comparisons of changes in OKT4/8

OKT4/8 was low in both groups before treatment; and was less than the normal level ($1.68 \pm 0.37$) in most patients. The values further decreased in both groups 1 months after operation, but increased gradually with the course of the treatment and returned to the normal level in most patients of the two groups. Some patients died without recovery of the value of OKT4/8, but no statistically significant difference was observed in the changes in OKT4/8 values between the two groups (Fig. 5). The changes in OKT4/8 for 24 weeks after operation were compared in 7 pa-
Fig. 5. Changes in OKT4/8 of patients both in the immunochemotherapy and the chemotherapy-alone groups

Fig. 6. Changes in OKT4/8 of more than 5 years — surviors both in the immunochemotherapy and the chemotherapy-alone groups
IMMUNOCHEMOTHERAPY FOR OVARIAN CANCER

TABLE 1
Patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Immunochemotherapy (n=22)</th>
<th>Chemotherapy (n=21)</th>
<th>χ² test</th>
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<tr>
<td>Histologic type</td>
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<tr>
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<td>15</td>
<td>NS</td>
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<tr>
<td>III</td>
<td>15</td>
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</tr>
<tr>
<td>IV</td>
<td>7</td>
<td>6</td>
<td></td>
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<tr>
<td>Median age</td>
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<td>54.1±8.7</td>
<td>NS (T test)</td>
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<td>PS</td>
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<td>6</td>
<td></td>
</tr>
<tr>
<td>3</td>
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<td>≥1cm</td>
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</tr>
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</tr>
<tr>
<td>Not performed</td>
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</table>

Patients who survived for 5 years or longer; (5 of there were in the immunochemotherapy and 2 in the chemotherapy group). The values returned to the normal range within 8 weeks after surgery in all patients of the former group, but the recovery was delayed until after 12 and 14 weeks in the latter group (Fig. 6).

Discussion

Ovarian cancer which metastasizes primarily by peritoneal dissemination, often spreads and diffuses early in the peritoneal cavity partly because of the thinness of the capsule of the organ. Also ovarian cancer occasionally grows to a very large mass rarely observed in cancer of other organs. For this reason, patients with ovarian cancer are considered to have immunological disadvantages as compared with cancer of other organs of the same stage.

From such a viewpoint, immunochemotherapy and the use of non-specific immunoadsorbers has been attempted for some time for the treatment of ovarian cancer. There have been some reports of its usefulness relative to chemotherapy alone. In most of these studies, however, histological types and clinical stages of the tumors were not evenly distributed among the subjects, and the therapeutic effects were compared only according to changes in immunological parameters.
The relative usefulness of the therapies must be evaluated by randomized controlled study in which uniformity of the age, histological types, clinical stages, and therapeutic methods is ensured, but such a study is often impossible in ovarian cancer, because it is difficult to accumulate a sufficient number of cases are difficult to accumulate in individual institutions. In Japan, multiinstitutional studies by Kanazawa et al. (1983) and Ohta et al. (1984) may be considered as including critical evaluations, but demerits of a joint study as suggested by the latter report are undeniable.

According to the present study, the survival of patients tended to be prolonged by the use of immunoactivators, although the difference was not significant. These results are consistent with the prolongation of the survival of patients with stage III and stage IV lesions reported by Ohta et al. (1984) and prolongation of survival (though not significant) in the case of stage II or more advanced cancer reported by Kanazawa et al. 1983. Moreover, in this study, immunochemotherapy was significantly more effective in the case of lesions 2 cm or greater in diameter. This result appears to correspond to the report by Yamamura et al. 1989 that OK-432 was effective in poorly differentiated non-curatively resected stomach cancer.

These results suggest that immunochemotherapy may be effective in more advanced cancer, which is associated with a large residual tumor volume and extremely high immunological risks. There are, however, reports that the therapy was effective in stage I and stage II lung cancer (Okayasu et al. 1989), only stage in II cervical cancer (Noda et al. 1989), and only in curatively resected stage III and IV stomach cancer but not in non-curatively resected lesions (Inaba et al. 1989). Causes of this discrepancy include differences in immunological environment of cancers of individual organs and differences in concomitant treatments.

We have reported that the ratio of OKT4+ cells to OKT8+ cells among peripheral lymphocyte subpopulation (OKT 4/8) most closely reflects the patients' immunological abilities (Hamai et al. 1985). In the present study, no significant difference was observed in the changes in OKT 4/8 between the two groups. However, in the 5 patients of the immunochemotherapy group and the 2 patients of the chemotherapy group who survived for 5 years or longer, the normal OKT 4/8 value was restored significantly more rapidly in the former group. The significance of this finding in the long-term with respect to survival remains a speculation. Whether or not immunological abilities are impaired or not during the second and third courses of induction chemotherapy, which is the most important period of the cancer therapy, may well have a major effect on clinical outcome. This speculation is supported by the finding that early death occurred more frequently in those patients of the chemotherapy group who showed delayed recovery of the immunological abilities.

Conclusion

It is probable that immunochemotherapy not only for ovarian cancer but also cancers of other organs should be performed in selected cases where the therapy can be expected to be effective rather than be applied at random. Our results suggest that lesions with larger residual tumor diameter are better indications for immunochemotherapy, and that immunochemotherapy may be expected to be also effective for recurrent ovarian cancer. Further evaluation is needed with
regard to the regimen of chemotherapy, number of its courses, and the timing of SLO.

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References


