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Short Communications

Comments on published articles, short communications of a preliminary nature, technical notes and the like are accepted under this heading. The articles should be short and concise and contain a minimum of figures, tables and references.

COMBINED INTERFERON AND VINBLASTINE TREATMENT IN ADVANCED RENAL CELL CANCER

Interferons (IFN) have been shown to have several antiviral, immunomodulatory, oncogene regulatory, and antiangiogenetic effects and to induce various enzymes. They increase expression of MHC class-I and -II antigens, and activate natural killer cells and macrophages. All of these effects are likely to facilitate the recognition and lysis of susceptible cells. However, the mechanisms that lead to destruction of cancer cells in the human body remain largely unknown (1).

Clinical trials of IFNs in cancer therapy began over 20 years ago. Favourable results have been achieved in the very rare cancer hairy cell leukaemia. In the commonest cancers (breast, lung, prostate) IFNs have not yet been shown to be effective. Ten to 20% of the patients with advanced malignant melanoma and renal cell cancer exhibited objective responses to IFN treatment (2–5). Most studies in renal cell cancer have been done with alpha-IFN. Doses of IFNs used in clinical studies have varied widely. Side effects have placed limits on dosage. The commonest side effects of IFNs are flu-like symptoms; malaise, chills, fever, anorexia, myalgia, arthralgia, neurological disorders, increases in liver enzyme levels, thrombopenia, leukopenia and anaemia (6, 7).

By combining interferons and chemotherapy, better responses (up to 45%) have been achieved than with IFN alone. In renal cell cancer, interferon has been used together with vinblastine, 5-fluorouracil and mitomycin-C (5, 7, 8–10). In a previous phase-II study one-third of our patients exhibited objective responses to combination therapy with interferon and vinblastine (11). However, the results of the only recent randomized study comparing IFN alone with a combination of IFN and vinblastine did not demonstrate any benefit in advanced renal cell cancer in comparison with IFN alone (8). Combination of IFN with other cytokines, e.g. IL-2, has proved no more effective than IFN and vinblastine (1, 12–14). Although some prolonged remissions have been achieved using IL-2 alone or combined with adoptive immunotherapy, the benefits of IL-2 therapy seem to be limited to patients in whom prognostic factors were initially good. IL-2-based combinations may cause many severe side effects.

The effects of IFN therapy on patients' survival in metastatic cancer are not yet certain. No dose schedule has yet been established and the optimum combination of IFN and other cancer treatments is not yet clear (13). The aim of the study reported here was to evaluate the efficacy and toxicity of treatment with IFN alpha-2a plus vinblastine in advanced renal cell cancer in a multi-centre study.

Materials and methods. Thirty patients under treatment at the departments of oncology and radiotherapy in three universities entered this phase-II trial from 1988 to 1989. The mean age of the patients was 57 years (range 38–75 years). Disease-free intervals varied from 0 to 64 months. One-quarter of the patients had metastatic disease at the time of primary diagnosis, and all patients had histologically verified advanced renal cell cancer. The metastatic sites are presented in the table. Seventeen patients (57%) exhibited more than one metastatic site. A nephrectomy was not performed on one patient.

The treatment schedule comprised vinblastine 0.1 mg/kg i.v. every third week and IFN alpha-2a (Roferon A) thrice weekly i.m. The first three doses of IFN alpha-2a were 3 MU. The third and fourth doses were 9 MU. From the fifth treatment onwards the dose was 18 MU. The safety and toxicity of treatments were evaluated every week during the first cycle and then every third week. During these visits side effects were surveilled by a physician, clinical status was assessed and blood samples and weight were taken. Response was evaluated every fourth week by clinical and radiological measurements. Both toxicity and response were classified in accordance with UICC guidelines (15). Both drugs can be administered to ambulant patients.

Results. Two cases of complete and five cases of partial response were observed, lasting for 6, 8, 9, 10, 11, 15, and 27 months. Twenty patients (67% of all the 30 patients) were alive one year after the start of the treatment. Thirteen patients (43%) survived for 2 years but only three patients were alive after three years. The median period of survival was 22 months. The organ exhibiting the best response was the lungs. The two patients who exhibited complete response had lung metastases. The third long-term survivor had liver metastases. Response was partial.

Non-evaluable patients were those who were treated for less than three weeks because of the side effects. In half of the patients the dosage had to be altered because of adverse events. Flu-like symptoms were the most common, and observed in 29 out of the 30 patients. Mental disorders were noted in five patients, of whom one experienced hallucinations. Mild or moderate leukopenia and anaemia were seen in over half of the patients. The other side events included arthralgia, myalgia and anorexia. Whether hepatotoxicity was related to treatment (with IFN alpha-2a and vinblastine) was impossible to determine, because paracetamol, which was used against the fever and flu-like symptoms, might have increased liver enzymes in two patients (6).

Discussion. The response rate of 6 out of 20 in renal cell cancer following IFN and vinblastine in a previous phase-II trial in Finland (11) was not achieved in the study reported here, conducted in three different hospitals. The overall response rate was 26%. Mean duration of response was 12 months. The results of this study, however, confirmed that the median survival period in renal cell cancer following this treatment is fairly lengthy. Both drugs can be delivered on an outpatient basis, and the treatment seems to be an improvement on the more aggressive and expensive combinations, such as high doses of interleukin-2 and adoptive immunotherapy (1, 2, 14). Many of the side-effects observed in this study surprised the investigators. Mental disorders were more common in one hospital than in the others and than in studies reported in the literature. The response rate and duration of survival were lower than in the previous report (11). This result might be due to the small sample size in both studies.

The best responses were achieved in relation to lung metastases in the study reported here, as in several previous studies (8, 11, 13). Although the response rate was only 26%, the median survival period was longer than those recorded in historical reports, or with other combinations including IL-2 based combinations. In a later study (14) where subcutaneous IL-2 and interferon were administered, the side effects were more severe, and the response rate was lower than in the study reported here. In the first randomized study (8) evaluating whether vinblastine plus IFN was more effective than IFN alone, the type of IFN and the treatment schedule differed from ours. In another randomized study (16) using the same treatment schedule as ours, the combination of IFN and vinblastine resulted in a doubling of response rate when compared to IFN alone. Their response rate was very similar to our response rate. However, the better response rate was not translated as indicating a better chance of survival. In addition there are several other reports of phase-II studies

Table

Patients' characteristics

Feature	Number of patients
Total number of patients	30
Mean age, years (range)	57 (38–75)
Gender, female/male	12/18
Disease-free interval	
No disease-free interval	7
<6 months	5
6–12 months	6
>12 months	10
>5 years	2
Metastatic sites	
Lungs	21
Liver	5
Bone	6
Soft tissue and others	9
One metastatic site	13
More than one metastatic site	17

combining IFN and VB, but it is difficult to compare the results, owing to different schedules and patient population. The response rate in those reports was at the same level as that in our study, namely between 10 and 25% (17, 18). Nor did combining VB and IL-2 lead to an increase in the response rate (19). The addition of VB only increased the myolotoxicity of the treatment (19). On the other hand, in the study by Patel & Lavengood (20) it is shown that about 70% of patients with metastatic renal cell cancer die within a year of diagnosis. In the study reported here the same percentage of patients survived for one year.

In the first reports of high-dose IL-2 by Rosenberg et al. (1) they achieved objective responses in one-third of the patients with RCC. Since then the other investigators have reported lower responses. Even the addition of lymphokine active killer cells or tumour infiltrating lymphocytes to IL-2 therapy has not yielded better response rates (21). The response rates have been at the same level as in the present study. Many more side effects have been associated with IL-2 therapy. A recent analysis of 425 patients (21) compared subcutaneous administration of IL-2 (SC) plus IFN to continuous intravenous administration of IL-2 (CIV). The overall response rate of CIV did not significantly differ from the SC regimens (15% versus 20% with 4% of complete responses in both arms). In this analysis there was an important shift in the toxicity profile. There was no capillary leak syndrome in the SC arm. In addition, SC treatment could be administered as outpatient therapy. However, the treatment with IL-2 and IFN is more expensive and more toxic than the treatment presented here. New ways of applying IL-2, such as the topical one, could be an interesting approach to better responses with fewer side effects (22).

In the literature there are reports of spontaneous disappearance of metastases in renal cell cancer, which have been linked with patients' own immunocompetence. However, the incidence of spontaneous remission is less than 1%. All our patients had progressive disease at the time of initiation of the treatment and it was not possible to follow them any further and so the treatment had to be instituted. It is no longer possible to carry out a placebo-controlled phase-III trial in advanced renal cell cancer because there are many treatment options, registered cytostatic drugs and cytokines, in the treatment of renal cell cancer and nowadays our patients are familiar with all of them. However, in older, good-risk patients, a 'wait and see' policy could be one option.

Whether there are benefits in terms of longer duration of survival from treating renal cell cancer patients with a combination of IFN and vinblastine, can only be determined in prospective, randomized studies.

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TUMOR CELL DNA CONTENT AND RADIATION RESPONSE IN HEAD AND NECK SQUAMOUS CELL CARCINOMA

DNA content in tumors is reported to be a prognostic factor in many malignancies. The presence of an abnormal stem cell line, termed aneuploidy, is generally accepted as a poor prognostic factor (1). However, some studies revealed that aneuploid tumors have a better response to radiation therapy. The prognostic value of DNA content has been debatable in head and neck cancer (1). In most of the reports paraffin-embedded material is used for the measurement of DNA content and the detection of aneuploidy might have been insufficient. In the present study, we examined cellular DNA content using fresh-frozen material in patients with head and neck cancer and made a prospective investigation of the relation between DNA content and treatment results.

Material and Methods. From August 1991 to January 1993, fresh-frozen materials from 45 patients with head and neck squamous cell carcinomas were examined for DNA content. Out of the 45 patients, 29 who were treated with definitive irradiation were studied on the relationship between DNA content and prognosis. The commonly used radiotherapy schedule was: 2.5 Gy per fraction with a total dose of 65 Gy and with an overall treatment time of 6.5 weeks. Mean follow-up period was 20 months. Primary sites were larynx in 10 (patients), paranasal sinus in 5, oropharynx in 5, tongue in 4, nasopharynx in 2, hypopharynx in 2 and buccal mucus in 1 patient. Measurement of DNA content was carried out using a flow cytometor (FACscan, Becton-Dickinson). Lymphocytes from healthy adults were used as controls for G0/G1 peak of the sample. The coefficient variance of the G0/G1 peak of the sample was 4.4 in its mean value. A DNA index (DI) was calculated from the DNA histogram. An aneuploid tumor was defined as having a DI of more than 1.1 or less than 0.9. The initial radiation response was assessed 2 months after the completion of treatment. Complete response (CR) was defined as disappearance of the tumor. Response to irradiation was based on physical examination and/or computed tomography.

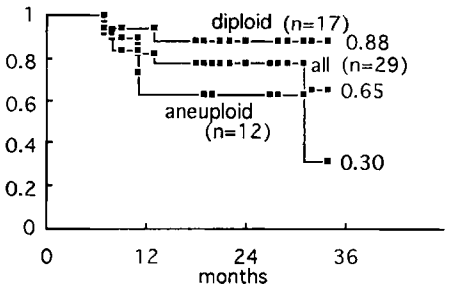

Figure. Survival by ploidy.

Results. All T1 and T2 tumors displayed a complete response regardless of the status of DNA content. Among 14 T3 or T4 tumors, CR was achieved in 8 cases. The mean value of DI in those 8 cases was higher than that of 6 residual cases, but there was no statistical significance. No difference in CR rate was found between aneuploid and dipioid tumors (63%(5/8) vs. 50%(3/6)). However, when the DI was set at 1.2 as the threshold, the CR rate was significantly higher above the threshold (100%(5/5)) than below (33%(3/9)) ($p<0.01$, χ^2-test). The Figure shows survival depending on ploidy. Aneuploid tumor cases showed poor survival and disease-free survival compared with those with diploid tumor though statistical significance was not indicated. A similar pattern could be seen in T3 and T4 cases.

Discussion. The prognostic value of tumor DNA content in squamous cell carcinoma has been controversial. Aneuploid tumors of the uterine cervix are reported to be more radiosensitive than diploid tumors (2, 3). Franzen et al. (4) studied 24 squamous cell carcinomas treated by radiotherapy, preoperatively. They reported that 5 of 7 aneuploid tumors were eradicated histologically by preoperative irradiation. However, Muller et al. (5) have reported that aneupoloid tumors had a poorer prognosis in a study of 50 patients with maxillo-facial carcinoma, who were given radiotherapy postoperatively. In the present study, aneuploid tumor, especially that with a large DI, tended to have a better response to radiotherapy. However, this initial improved response did not lead to a better chance of survival in cases of aneuploid tumor. The reason for this was that recurrence or residual disease in aneuploid cases could not be salvaged, whereas recurrences or residual disease in diploid cases tended to stay at the primary site and did not display rapid growth. These were effectively salvaged by surgery. Recently, it was reported that aneuploid tumors have greater proliferlative activity than diploid tumors in head and neck SCC (6). Dyson et al. (2) reported that aneuploid tumors quickly spread locally and metastasize to other organs. Our findings were consistent with these studies. To conclude, aneuploid tumors seem to be radiosensitive but have a poor prognosis in head and neck squamous cell carcinoma.

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