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UFT for head and neck cancers: its tissue concentrations and effects on lymphocyte subpopulations

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Summary. UFT, a combination of the masked compound of 5-fluorouracil (FT-207) and uracil, was given to head and neck cancer patients for 1 week preoperatively and for 8 weeks postoperatively. Drug concentrations were examined in the surgically removed tissues. The concentrations of FT-207, 5-fluorouracil, and uracil were higher in tumor tissues than in normal tissues. The lymphocyte subpopulations were assessed by cytofluorometry with monoclonal antibodies. There was no evidence that adjuvant chemotherapy with UFT specifically suppresses immunocompetent cells. We therefore conclude that further clinical evaluation of adjuvant chemotherapy with UFT would be worthwhile.

Introduction

Both drug factors and host factors should be taken into consideration to maximize that effectiveness of anticancer agents while minimizing their side-effects. This requires a high drug concentration in the cancer tissue, and a low concentration in normal tissues and blood [4]. One approach to meeting these two conflicting requirements is to combine two kinds of drugs, such as an antimetabolite and a metabolite. UFT, a compound consisting of 4 parts of uracil to 1 part of a masked compound of 5-fluorouracil (5-FU), FT-207 (1-(2-tetrahydrofuryl)-5-fluorouracil, Tegafur), has been reported to be one such drug [1, 2].

Growing evidence suggests that the cellular immunity of the host is an important factor in both the genesis and the treatment of cancers. Unfortunately, some anticancer agents suppress cellular immunity. Although UFT is reported to have little inhibitory effect on cell-mediated responses in mice [9], corresponding information for humans is lacking. We therefore examined the tissue concentrations and effects on lymphocyte subpopulations of UFT in head and neck cancer patients.

Materials and methods

Subjects. The subjects were 32 patients suffering from cancer of the head and/or neck region, who had been operated on in our department between February and August, 1984. There were 2 patients in their thirties, 4 in their forties, 7 in their fifties, 11 in their sixties, and 8 in their seventies. The cancers were of the larnyx (13 cases), oral cavity (7 cases), tyroid (6 cases), hypopharynx (3 cases), nasal cavity and paranasal sinus (1 case), mesopharynx (1 case), and salivary gland (1 case). By histological type, there were 25 cases of squamous cell carcinoma, 2 of adenoid cystic carcinoma, and 2 of adenocarcinoma; in 3 the histological type was uncertain. The patients' overall condition in terms of performance status was zero for 30 cases, 1 for 1 case and 2 for 1 case. Postoperative telecobalt irradiation with 3000–12000 rads was performed in 24 patients.

Administration method. UFT was given for the 7 days before the operation at a dose of 600 mg/day. After surgery, administration was resumed following recovery. It was usually continued for 2 weeks.

Assay of serum and tissue drug concentrations. Serum and tissue samples were obtained from patients at the time of operation. The period between the last drug administration and sampling varied from 12 h to 19 h. Based on the histological examination of the specimens, the samples were divided into tissues with cancer infiltration and tissue with no such infiltration (normal tissue). After the blood had been removed from each tissue sample as far as possible by wiping, tissues were frozen and stored. The tissues thus classified were then checked by pathological tests for possible cancer infiltration. Measurement of the frozen serum and various tissues was done by HPLC for FT-207 according to Marunaka et al. [5], and that of 5-FU and uracil by gas-mass chromatography [8].

Assay of lymphocyte subpopulations in the peripheral blood. Heparinized blood (3-ml samples) was collected before UFT administration, just before operation, 1 week after operation, before resumption of drug administration and every 4 weeks thereafter. For T cell assay, 100 µl blood sample was combined with 100 µl phosphate-buffered saline (PBS) and 10 µl FITC-labelled monoclonal antibodies. The antibodies used were OKT3, OKT4 and OKT8 (Ortho Diagnostic systems Inc., Raritan, NJ, USA) for total T cells, T helper/inducer cells and T suppressor/cytotoxic cells, respectively. The samples were incubated in an ice bath for 30 min, with agitation every 10 min. After the

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addition of 2 ml lysing agent, the solution was incubated at 37 °C for 5 min and centrifuged. The precipitate was suspended in 2 ml PBS and injected into a flow cytometry system (Ortho, Spectrum III). For B cell assays 100 µl blood sample was combined with 100 µl of PBS and 5 µl OKIa1 monoclonal antibody (Ortho). The sample was incubated in an ice bath for 30 min, with agitation every 10 min. After washing with 2 ml PBS twice, the sample was incubated with 50 µl anti-mouse IgG FITC in ice bath for 30 min, with agitation every 10 min. The sample was thereafter treated as for T cell assays. These assays was performed at the Otsuka Assay Research Center in Tokushima, Japan. The data were given as mean ±SD

Results

Serum and drug concentrations within tissue

Figures 1–3 show the respective FT-207, 5-FU and uracil concentrations in each type of tissue after 7 days UFT administration, at the final administration 15–21 h before surgery.

The concentration of FT-207 in cancerous tissues was 4.75±3.56 µg/g; in metastasizing lymph node [LN(+)], 3.14±1.63 µg/g; in non-metastasizing lymph node [LN(−)], 2.92±1.48 µg/g; in muscles, 3.66±1.85 µg/g; in skin, 2.88±1.95 µg/g; and in other normal tissue, 3.65±2.94 µg/g. The serum concentration of FT-207, at 9.45±7.53 µg/ml, was high, while the levels in the other tissue were virtually the same (Fig. 1).

The concentration of the active form of 5-FU in the cancerous tissues (0.144±0.181 µg/mg) was almost 14.4-fold higher than that in the serum (0.01±0.008 µg/ml), which was a significant difference ($P<0.0003$). The level in the cancerous tissue was nearly 5 times ($P<0.003$) that in the muscle (0.029±0.039 µg/g) or skin (0.03±0.037 µg/g) and was 2.4-fold higher ($P<0.03$) than that in other normal tissue (0.061±0.061 µg/g) (Fig. 2).

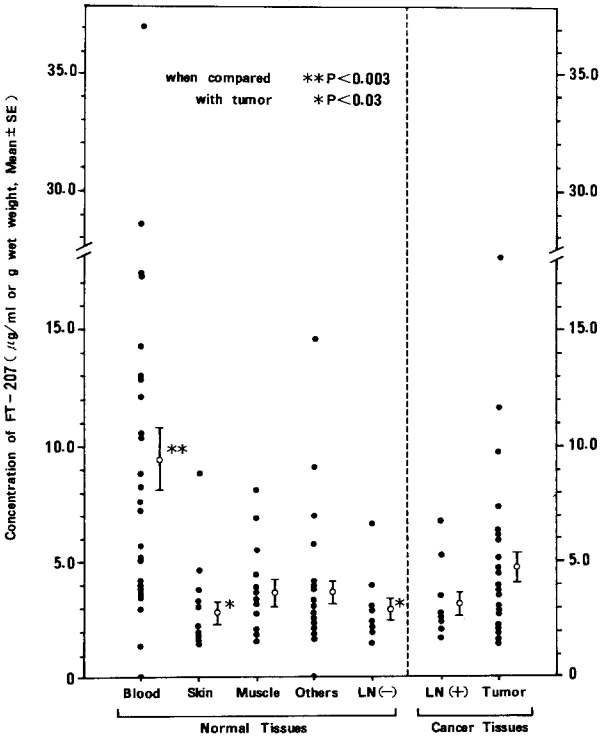

Fig. 1. FT-207 concentration after UFT administration *LN(−)*, non-metastasizing lymph node; *LN(+)*, metastasizing lymph node; UFT was given for 7 days, 600 mg/day, p.o.

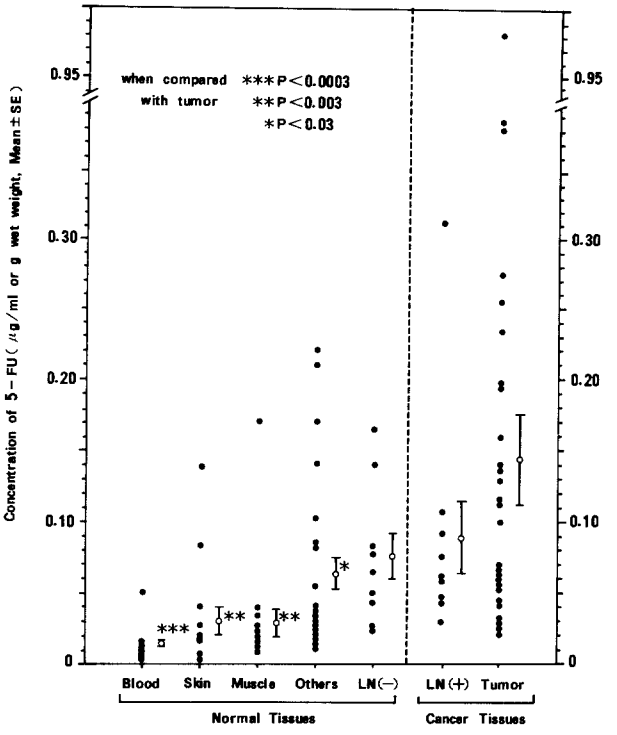

Fig. 2. 5-FU concentration after UFT administration. Abbreviations as for Fig. 1

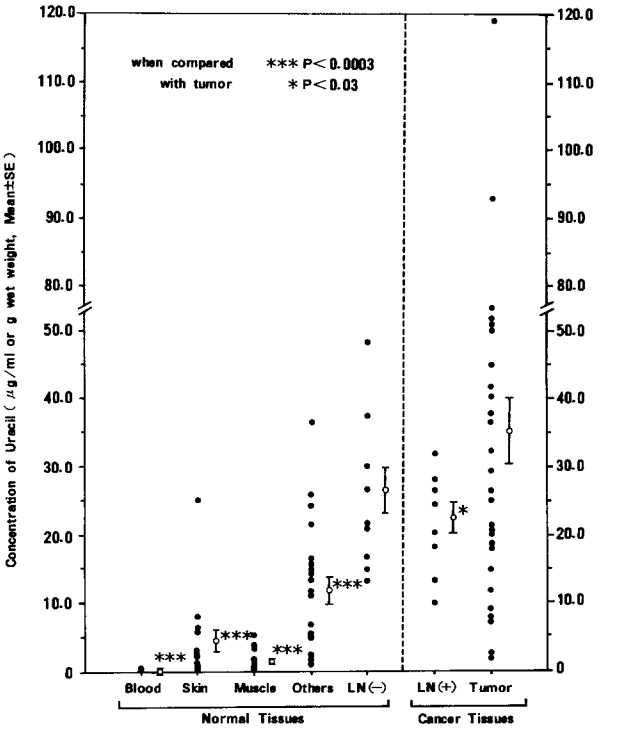

Fig. 3. Uracil concentration after UFT administration. Abbreviation as for Fig. 1

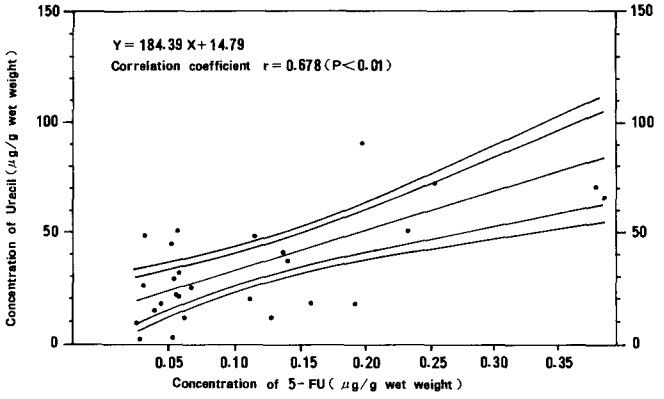

Fig. 4. Linear regression and correlation coefficiency between 5-FU and uracil concentrations

The concentration of uracil was high in cancerous tissues (35.15 ± 27.21 μg/g) and low in the muscle (1.51 ± 1.39 μg/g), skin (4.43 ± 6.35 μg/g), other normal tissue (11.67 ± 9.55 μg/g), and serum (0.04 ± 0.12 μg/g) (Fig. 3).

The 5-FU and uracil concentrations in the cancerous tissues showed a linear regression and correlated well (coefficient, 0.678) with statistical significance ($P < 0.01$) (Fig. 4).

Effects on lymphocyte subpopulations in the peripheral blood

No significant change in lymphocyte subpopulation was observed throughout the investigation period (Table 1); hence the ratio of OKT4-positive to OKT8-positive cells (helper cell-to-suppressor cell ratio) remained unchanged. In some cases the lymphocyte subpopulations were assayed up to 30 weeks after the surgery; even at this point they were still unchanged.

Discussion

At present, surgical intervention still assures the best results of any sort of therapeutic treatment for cancer. However, chemotherapy remains a necessary adjuvant to surgical treatment. For better chemotherapy, an anticancer agent that is more toxic to cancer tissues and less toxic to normal tissues, including immunocompetent cells, is required.

UFT, a compound consisting of 4 parts of uracil to 1 part of a masked compound of 5-FU (FT-207), is such a drug. 5-FU is metabolized by two pathways. One is degradation to an inactive form and the other is phosphorylation. The phosphorylated compounds inhibit DNA synthesis and are cytotoxic. Degradation is more active than phosphorylation in the normal tissues, while the situation is reversed in the tumor. Furthermore, uracil is known to inhibit degradation but not phosphorylation. Therefore, the combination of 5-FU or its masked compound and uracil should increase the concentration of 5-FU in tumor tissue but not in normal tissue. The optimal combination ratio was determined experimentally [1, 2, 7].

Our findings prove the validity of the theory in head and neck cancers. The concentrations of both FT-207 and 5-FU were higher in the tumor tissue than in normal tissues, although the value varied from low to high depending on the cases (Fig. 1, 2). The fact that uracil is concentrated in tumor tissues may contribute to the higher concentration of 5-FU in these tissues, since uracil is known to inhibit the degradation of 5-FU. The positive correlation between the concentrations of 5-FU and uracil in cancer tissues supports this possibility.

No significant alteration of lymphocyte subpopulation was observed during the test period. This means that not only the adjuvant chemotherapy with UFT but also the surgical procedure and irradiation caused neither suppression nor enhancement of a specific subpopulation during the observation period.

From these results we conclude that further clinical evaluation of adjuvant chemotherapy with UFT is worthwhile. In fact, since the concentrations of both FT-207 and 5-FU in tumor tissue varied widely and since the concentrations in lymph nodes with metastasis did not differ significantly, we definitely need to evaluate the clinical responses of our cases before we conclude the clinical effectiveness of UFT. Trial use of UFT to head and neck cancers was decisively effective (20%–30%) [3, 6].

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Table 1. Time-course of lymphocyte subpopulations in the peripheral blood during adjuvant chemotherapy with UFT

	OKT 3 (Total T cells)	OKIa 1 (Total B cells)	OKT 4 (T helper/ inducer cells)	OKT 8 (T suppressor/ cytotoxic cells)	OKT 4/OKT 8
1. Before UFT administration	63.84± 9.13	22.31± 8.38	40.18± 8.97	29.00± 9.68	1.63± 0.87
2. Just before operation	61.91±10.63	20.79±10.96	37.69± 8.52	30.21±10.80	1.49± 0.87
3. One week after operation	64.23± 9.61	19.37± 8.54	40.30± 8.74	28.49±11.61	1.71± 0.90
4. At resumption of UFT administration	65.33±10.23	19.88±11.53	40.69±10.15	28.66±11.78	1.70± 0.89
5. Four weeks later	62.30±11.52	20.75±10.32	38.34±11.19	29.73±11.33	1.53± 0.88
6. Eight weeks later	62.02±12.36	18.75± 9.03	36.54±11.48	31.16±13.55	1.44± 0.78

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