Alterations of Intratumoral Pharmacokinetics of 5-Fluorouracil in Head and Neck Carcinoma during Simultaneous Radiochemotherapy

Heinz-Peter Schlemmer, Markus Becker, Peter Bachert, Andreas Dietz, Volker Rudat, Bernhard Vanselow, Petra Wollensack, Iwan Zuma, Michael V. Knopf, Hagen Weidauer, Michael Wannenmacher, and Gerhard van Kaick

Research Program Radiological Diagnostics and Therapy, German Cancer Research Center (Deutsches Krebsforschungszentrum) [H.-P. S., M. B., P. B., I. Z., M. V. K., G. v. K.], and Departments of Otolaryngology, Section Oncology [A. D., B. V., P. W., H. W.], and Radiation Therapy, Radiological Clinic [V. R., M. W.], University of Heidelberg, 69120 Heidelberg, Germany

ABSTRACT

The kinetics of local drug uptake and metabolism of the anticancer drug 5-fluorouracil (5-FU) has been monitored by means of 19F nuclear magnetic resonance spectroscopy in 17 patients with neck tumors during concurrent radiochemotherapy. All of the patients underwent an accelerated hyperfractionated, concomitant-boost radiochemotherapy with 5-FU [600 or 1000 mg/m² of body surface (b.s.)] and carboplatin (70 mg/m² of b.s.). Serial 19F nuclear magnetic resonance spectra were obtained during and after the administration of 5-FU in a 1.5T scanner with the use of a 5-cm diameter surface coil positioned on a cervical lymph node metastasis. Examinations were performed at day 1 of therapy and, in 13 patients, also after 43.5 Gy of irradiation at day 1 of the second chemotherapy cycle. Resonances of 5-FU and the catabolites 5,6-dihydro-5-fluorouracil (DHFU) and α-fluoro-β-alanine (FBAL) were resolved in the tumor spectra. The median of the 5-FU and FBAL levels was significantly higher (more than 2-fold) at the second compared with the first examination, whereas the level of DHFU did not change. This effect could indicate an increased delivery of 5-FU into the interstitial space of the tumor in the course of the combined treatment, which would result in an enhanced exposure of the tumor cells to the drug. A potential mechanism for synergy between radio- and chemotherapy is discussed, but alternative mechanisms are also being considered. The findings indicate that a method is available to rationally address the design of dosing schedules in concurrent therapy regimens.

INTRODUCTION

5-FU\(^{\text{1}}\) is one of the most promising drugs applied in concurrent radiotherapy and chemotherapy of different malignancies (1–5). However, little is known about the underlying mechanisms of the interaction of ionizing radiation and 5-FU chemotherapy (6, 7). In particular, it is not clear whether the effect is additive or synergistic. On the basis of in vitro studies, different cellular and molecular mechanisms of fluoropyrimidine-radiation interaction have been discussed, e.g., the induction of cell-cycle redistribution, the interference of nucleotide pools, or the incorporation of 5-FU anabolites into DNA (8). The major interest focuses on the influence of chemotherapy on the effect of radiotherapy. Conversely, one may ask how irradiation affects the pharmacokinetics of 5-FU. Recent data from in vivo 19F-NMR experiments in animals indicate a prolonged retention of this drug in tumor tissue induced by irradiation (9). Presently, no clinical studies are known that investigate whether irradiation affects the intratumoral pharmacokinetics of 5-FU in patients undergoing standard treatment protocols.

Fluorine-19 NMR spectroscopy permits noninvasive monitoring of the pharmacokinetics of 5-FU in vivo (10–12). The 19F nucleus has 100% natural abundance and a NMR sensitivity comparable to that of \(^{1}\)H. There is no 19F-NMR background signal from the tissue because the physiological concentration of mobile fluoride (less than \(10^{-6}\) M) is below the detection threshold. The large chemical shift range allows the spectral resolution of NMR signals of 5-FU and different 5-FU metabolites even at the relatively low field strength of 1.5 T commonly used for clinical NMR spectroscopy. Previous 19F-NMR studies with human patients undergoing 5-FU chemotherapy, which focused mainly on the examination of liver metastases, indicate a correlation of intratumoral 5-FU levels and response to treatment (13–15).

The aim of our clinical study was to detect possible changes of intratumoral 5-FU pharmacokinetics in patients in the course of simultaneous radiotherapy and chemotherapy. For this purpose, 19F-NMR spectroscopy examinations were performed in patients with advanced head and neck carcinomas. Randomized clinical trials indicate that radiochemotherapy using 5-FU in combination with other drugs, particularly cisplatin, improves therapeutic outcome of head and neck cancer in terms of improved locoregional control, disease-free survival, and overall survival rates (5). We present what we believe to be the first report on 19F-NMR-monitored intratumoral pharmacokinetics of 5-FU in patients undergoing a simultaneous radiochemotherapy.

MATERIALS AND METHODS

Patients. Seventeen patients (3 female, 14 male) with previously untreated, unresectable SCCs of the head and neck were included in this study. The mean age of the patients was 53.4 years (range, 39–76 years). Primary tumors were located at the oro- and hypopharynx and mainly presented in stage IV (16) before the beginning of therapy. The volume of the examined cervical lymph node metastases (\(V_m\)) was approximated by an ellipsoidal shape:

\[
V_m = \frac{\pi}{6} (d_x \times d_y \times d_z)
\]

where \(d_x\), \(d_y\), and \(d_z\) are orthogonal diameters that are measured by means of diagnostic imaging. The median of the tumor volumes determined in this way was 11.5 cm\(^3\) (range, 1.2 cm\(^3\) to ~500 cm\(^3\)). Detailed patient data are given in Table 1.

The treatment included an accelerated hyperfractionated radiotherapy using a concomitant-boost technique and simultaneous chemotherapy with 5-FU and carboplatin. A total radiation dose of 69.9 Gy was applied within 38 days. The primary tumor and the locoregional lymph nodes were irradiated at a dose of 1.8 Gy/day on days 1–5 in weeks 1–5 and on days 1–3 in week 6. In weeks 4, 5, and 6, a concomitant boost of 1.5 Gy was applied to the tumor as a second daily dose. All of the patients were treated in a thermoplastic mask for...
immobilization. Between two daily fractions, there was a minimum time interval of 6 h in each case.

The definitions of the target volumes were based on CT or magnetic resonance imaging scans in all of the patients, and the dose was calculated to midplane using the custom-developed software “Ziviplan Heidelberg.” With the use of 6-MeV photons, the primary tumor including a safety margin and the upper and middle neck nodes were irradiated through parallel opposed fields, and the lower neck nodes were irradiated with an anterior oppositional field. The patient died from tumor bleeding.

Two cycles of chemotherapy with 5-FU (dose, 600 or 1000 mg/m² of b.s. × day) and carboplatin (70 mg/m² of b.s. × day) were applied on days 1–5 (week 1) and days 29–33 (week 5). Tumor response was assessed 6 weeks and the lower neck nodes were irradiated with an anterior oppositional field.

Individual blocks were used to spare healthy tissue as far as possible. With a dose of 27 Gy at the isocenter, the spinal cord was outside the photon fields. The uninvolved posterior neck was treated according to CT findings with electrons of selected energy using a dose of 2.5 Gy/day applied five times a week (total dose, 55 Gy). The boost comprising the macroscopic tumor was delivered by opposed lateral fields.

Two cycles of chemotherapy with 5-FU (dose, 600 or 1000 mg/m² of b.s. × day) and carboplatin (70 mg/m² of b.s. × day) were applied on days 1–5 (week 1) and days 29–33 (week 5). Tumor response was assessed 6 weeks and 3 months after therapy by determining the tumor size from CT or ultrasonographic images. Response was finally classified according to the WHO criteria as complete remission (CR, complete disappearance of the tumor), partial remission (PR, reduction of tumor size by 50% or more), stable disease (SD, reduction of tumor size by less than 50% or increase of tumor size by less than 25%), and progressive disease (PD, increase of tumor size by more than 25%).

A 1-pulse-acquire sequence was used for fluorine signal detection. Individual transients of 1024 (1 K) complex data points were accumulated over a 21-kHz spectral window using a 150-μs excitation pulse width and a signal acquisition time of 35 ms. The delay between pulse and data collection was 500 μs, and repetition time was 38 ms. Each 19F-NMR spectrum was recorded with the number of excitations equal to 9300, resulting in a temporal resolution of 6 min for monitoring the kinetics.

For a comparison of 5-FU uptake and metabolism at the various stages of treatment, 19F-NMR spectra were analyzed in two different ways: (a) for the kinetic analysis, FIDs nos. 1, 2, 3, and so forth, obtained during and after 5-FU administration were added according to: 1, 1

\[1 \times 1\] , 1

\[2 \times 1\] , 1

\[3 \times 1\] , and so forth (cumulative sum); and (b) the sum of FIDs acquired during the infusion period (50 min) was used to estimate the amount of 5-FU and of fluorine-containing metabolites present in the tumor tissue during 5-FU administration. The resulting time-domain signals were zero-filled to 8 K data points and apodized by an exponential (τ⁻¹ = 10 Hz) and a Gaussian function (τ⁻¹ = 0.01 Hz) before Fourier transformation and phase correction. The combination of exponential and Gaussian function provides optimum S:N on condition of minimum line-broadening. After base-

Classification of response according to TNM (tumor, node, metastasis) system (16).

Volume changes of examined lymph node metastases classified according to WHO criteria: PR, partial remission (reduction of tumor size by 50% or more); CR, complete remission (complete disappearance of the tumor); SD, stable disease (reduction of tumor size by less than 50% or increase of tumor size by less than 25%); PD, progressive disease (increase of tumor size by more than 25%).

A rough estimate in the case of large lymph node conglomerates.

Not evaluated.

Not evaluated after 3 months; the patient developed cutaneous filiae 2 months after treatment.

Not evaluated.

The patient died from tumor bleeding.

Fluorine NMR. 19F-NMR spectroscopy was performed in a 1.5-T whole-body scanner (Magnetom 63/84 SP; Siemens, Erlangen, Germany) on days 1 and 29 of treatment (i.e., on day 1 of the first and second chemotherapy cycle). A 5-cm-diameter surface coil (built by H-J. Zabel, Deutsches Krebsforschungszentrum) tunable to 1H (for shim on the tissue water 1H resonance) and 19F Larmor frequency was positioned centrally on a palpable neck metastasis (Fig. 1).

To ensure reproducibility in repeat measurements, the positioning of the coil on the tumor as well as the coil’s orientation relative to the direction of the magnetic field were carefully recorded for each patient. The individual 5-FU dose was diluted in a 250-ml solution of 0.9% sodium chloride and administered i.v. at an infusion rate of 5 ml/min (total infusion time, 50 ± 2 min). A series of 19F-NMR spectra was acquired during 5-FU administration. In the case of good cooperation of the patient, additional spectra were recorded for a period up to 30 min after the end of the infusion. Repeat examinations were performed only on patients exhibiting fluorine signals on the first examination (except patient no. 14).

Fig. 1. Transversal, contrast-enhanced spin-lattice relaxation time weighted (T₁w) image showing a large lymph node metastasis of an oropharynx/tongue base carcinoma on the left neck side of patient no. 12. Bracket, the position of the 5-cm-diameter 19F surface coil. Scale marker, 10 cm.
Table 2. Chemical shifts and assignments of resonances resolved in $^{19}$F-NMR spectra of neck tumors in 17 patients undergoing radio/[5-FU+carboplatin] chemotherapy

<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical shift, δ (ppm)</th>
<th>Linewidth, Δν/2 (Hz)</th>
<th>Reference, δ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU</td>
<td>-93.7 ± 0.2</td>
<td>60 ± 5</td>
<td>-93.77</td>
</tr>
<tr>
<td>FBAL</td>
<td>-112.7 ± 0.3</td>
<td>110 ± 10</td>
<td>-112.77</td>
</tr>
<tr>
<td>DHFU</td>
<td>-126.3 ± 0.3</td>
<td>85 ± 8</td>
<td>-126.27</td>
</tr>
</tbody>
</table>

* Unassigned peaks with unknown origin at δ = -133.8 ± 0.5 ppm and δ = -137.7 ± 0.5 ppm.
* Chemical shift versus TFA in H$_2$O (δ = 0); mean ± SD.
* Full width at half maximum; mean ± SD.
* High-resolution in vitro NMR measurement at 11.7 T and 28°C (19).

RESULTS

Thirty $^{19}$F-NMR examinations were carried out in this study. Thirteen of 17 patients were examined twice, i.e., during their first and second cycle of chemotherapy. Four patients (nos. 7, 9, 11, and 13) underwent only one $^{19}$F-NMR examination.

Broad $^{19}$F-NMR resonances of 5-FU [chemical shift position (δ) = -93.7 ppm; linewidth (Δν/2) = 60 Hz], FBAL (δ = -112.7 ppm, Δν/2 = 110 Hz), and DHFU (δ = -126.3 ppm, Δν/2 = 85 Hz) were found in the tumor spectra (Table 2 and Fig. 2). The signal of 5-FU was observed in the spectra of 11 of 17 patients and in 21 of 30 examinations. A comparison of tumor volumes in Table 1 and of 5-FU PHARMACOKINETICS DURING RADIOCHEMOTHERAPY.

DISCUSSION

The intracellular metabolism of 5-FU is complex as elucidated in a large number of biochemical and in vitro and in vivo NMR studies. A review of 5-FU biochemistry and pharmacology is given in Ref. 17. The anticancer effect of the drug is attributed to two different mechanisms: (a) the inhibition of the enzyme thymidylate synthase (EC 2.1.1.45) by the anabolite 5-fluoro-UMP; and (b) the interference of maturation of rRNA because of the incorporation of 5-fluoro-UTP.

The detoxification of 5-FU takes place mainly in the liver. In the
In the treatment of head and neck carcinomas, higher response rates were observed when 5-FU was administered via continuous infusion in contrast to bolus injection (20). The combination of radiotherapy and 5-FU chemotherapy showed positive effects when ionizing radiation and the drug were applied concurrently. No benefit was seen when 5-FU alone or in combination with other drugs was administered before or after radiotherapy, e.g., as induction or adjuvant therapy (5). This agrees with the results of in vitro experiments, which showed that 5-FU has to be present in the tumor tissue for at least 24 h after irradiation to produce a radiosensitization effect (18).

After the pioneering 19F-NMR examinations of patients by Wolf et al. (11), several clinical studies have been performed to monitor 5-FU pharmacokinetics during chemotherapy. After bolus infusion, the intratumoral half-life (t_{1/2}) of 5-FU was determined (21). Findlay et al. (13) and Schlemmer et al. (15) estimated drug and metabolite levels after continuous and 10-min i.v. infusion of 5-FU, respectively. These studies showed that t_{1/2} \leq 20 min of free 5-FU in malignant tumors (“trapping”; 21) as well as enhanced intratumoral 5-FU levels are predictive of a therapeutic response (13–15).

### Table 3: Normalized 19F-NMR signal intensities of 5-FU and catabolites in the sum of spectra acquired during the 5-FU infusion period

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>5-FU dose (mg/m² b.s. day)</th>
<th>Examination</th>
<th>t^m_5-FU</th>
<th>t^m_DHFU</th>
<th>t^m_FBAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>600</td>
<td>1</td>
<td>6.7</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1000</td>
<td>1</td>
<td>4.0</td>
<td>3.6</td>
<td>2.2</td>
</tr>
<tr>
<td>3</td>
<td>1000</td>
<td>1</td>
<td>8.0</td>
<td>2.0</td>
<td>3.0</td>
</tr>
<tr>
<td>4</td>
<td>600</td>
<td>1</td>
<td>10.1</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>600</td>
<td>1</td>
<td>15.4</td>
<td>1.6</td>
<td>2.8</td>
</tr>
<tr>
<td>6</td>
<td>600</td>
<td>1</td>
<td>1.9</td>
<td>0.7</td>
<td>1.3</td>
</tr>
<tr>
<td>7</td>
<td>600</td>
<td>1</td>
<td>5.3</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>600</td>
<td>1</td>
<td>11.5</td>
<td>3.2</td>
<td>4.0</td>
</tr>
<tr>
<td>9</td>
<td>600</td>
<td>1</td>
<td>2.9</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>600</td>
<td>1</td>
<td>4.2</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>600</td>
<td>1</td>
<td>1.5</td>
<td>4.3</td>
<td>1.2</td>
</tr>
<tr>
<td>12</td>
<td>1000</td>
<td>1</td>
<td>30.1</td>
<td>5.3</td>
<td>4.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>59.1</td>
<td>3.5</td>
<td>6.5</td>
</tr>
<tr>
<td>13</td>
<td>600</td>
<td>1</td>
<td>1.2</td>
<td>1.9</td>
<td>1.5</td>
</tr>
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<td>600</td>
<td>1</td>
<td>4.1</td>
<td>3.3</td>
<td>4.9</td>
</tr>
<tr>
<td>15</td>
<td>600</td>
<td>1</td>
<td>1.3</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>16</td>
<td>600</td>
<td>1</td>
<td>4.9</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>600</td>
<td>1</td>
<td>1.3</td>
<td>0.8</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>4.1</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td>1</td>
<td>2.40</td>
<td>1.25</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>6.65</td>
<td>1.25</td>
<td>1.95</td>
</tr>
</tbody>
</table>

*Infusion time of first examination, 35 min.
One NMR examination only.
Infusion rate, 4 ml/min; infusion time, 78 min.

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First step, the drug is reduced to DHFU by trans-addition of two hydrogen atoms to the C⁵=CH⁶ double bond under consumption of energy. The degradation further proceeds to FUPA and FBAL. FBAL, the most abundant 5-FU metabolite in the body during 5-FU chemotherapy, is finally excreted via the kidneys.

In vitro and in vivo animal studies indicate that 5-FU acts as a radiosensitizer, but the underlying mechanism is poorly understood (6, 7). In experiments on cell cultures, Byfield (18) found three prerequisites for radiosensitization owing to 5-FU: (a) the tumortoxicity of the drug; (b) a sufficient amount of 5-FU the tumor cells are exposed to; and (c) the presence of the drug in the tumor tissue for at least 24 h after irradiation.

Although in vitro models, e.g., isolated tumor cells, permit study of the mechanisms of the interaction of 5-FU and ionizing radiation, important environmental factors that are effective in tumors in situ cannot be assessed in these systems. The amount of 5-FU that reaches the tumor cells depends on different mechanisms that are not directly related to the administered 5-FU dose. The major fraction of the infused drug is rapidly eliminated from the plasma by the catabolism in the liver. Although the plasma concentration of 5-FU could be relevant to the amount of 5-FU that reaches the tumor cells, plasma and urine levels of 5-FU and 5-FU metabolites of individual patients—determined ex vivo by means of high-resolution 19F-NMR spectroscopy—did not correlate with tumor response to treatment (19). However, the intratumoral accumulation and retention of 5-FU, which was first measured by C. A. Presant et al., was found to be related to response to chemotherapy (14). This result demonstrates the importance of the in vivo determination of intratumoral 5-FU levels.
In the present study, spatial localization of 19 F-NMR signals in neck metastases was performed by means of a small surface coil, which is adequate for the examination of superficial tumors. The simultaneous measurement of the reference signal allowed the control of the coil’s sensitivity as well as the quantitative comparison of drug and catabolite signals from different examinations. Because in most of the 6-min spectra the available signal was poor, FIDs were added to enhance S:N and to reduce errors in the statistical analysis. Although the resulting sum spectra showed sufficient S:N for the evaluation of relative signal intensities, a quantitative estimation of the 5-FU concentration in the tumors was difficult. Taking into account the sensitive volume of the surface coil (approximately \(2\pi R^2/3 \approx 33 \text{ cm}^3\); \(R\) = radius of the coil’s loop) and assuming a homogeneous distribution of the drug in the tissue, the minimum 5-FU concentration \(c_{\text{min}}\) that can be detected within a 6-min measurement time with our equipment is \(c_{\text{min}} \equiv 30 \mu M\) as estimated from experiments on model solutions. However, absolute quantification by in vivo NMR is generally difficult because tumors are different in size and inhomogeneous, and, technically, fully relaxed spectra cannot be acquired when the measurement time is limited.

The frequent and repeated detection of DHFU in this work was surprising. Previous patient studies indicated that the tissue concentration of this intermediate of 5-FU catabolism is generally below the NMR detection limit (Refs. 11, 22; an exceptional case with a detectable level of DHFU in the metastatic liver is reported in Ref. 15). Because the concentration of free DHFU in plasma is too low for

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19F-NMR detection in vivo (19), the signal at δ = −126.3 ppm could originate from DHFU produced by the tumor cells. This interpretation agrees with in vitro experiments, which showed that DHFU is the major 5-FU catabolite in SCCs (23).

High steady-state concentrations of DHFU are possible if the transition from DHFU to FUPA/FBAL is rate-limiting. This agrees with the observation that, in patients with detectable FBAL and DHFU levels, the DHFU signal appeared before the FBAL signal (Figs. 3 and 4). Although DHFU is a catabolite of 5-FU, its detection in tumor tissue could be important (24). The intermediate is cytotoxic as shown in vitro. Presumably, DHFU is converted back to 5-FU and acts as a storage form of 5-FU (25).

FBAL was observed less frequently. The peak at δ = −112.7 ppm was significantly broader than the 5-FU resonance and unresolved in agreement with spectra obtained in previous in vivo 19F-NMR studies (11, 22). There are two reasons for the broadening of this resonance: (a) the scalar spin-spin coupling of 19F and 1H nuclei in FBAL which causes a multiplet splitting into eight resonances (19, 26); and (b) signal overlap owing to the small chemical shift difference of only 1.8 ppm of FBAL and its precursor in the catabolic pathway, FUPA [according to high-resolution experiments in vitro (19)]. The peak assigned to FBAL may, therefore, contain a signal contribution of FUPA. Because 5-FU catabolism mainly takes place in the liver, the signal at δ = −112.7 ppm will first be related to FBAL, which is produced in the hepatocytes and thereafter transported to the examined tumor region by the blood. A distinct signal contribution from FBAL formed in SCC is less probable. In particular, experiments with human SCC cell lines performed by Spoelstra et al. (23) showed that only a very small amount of FBAL is produced by the tumor cells.

The significantly higher intensities of 5-FU at the beginning of the second cycle compared with the first cycle of chemotherapy (after 4 weeks of radiotherapy and a total dose of 43.5 Gy) point to alterations of 5-FU pharmacokinetics in the examined lymph node metastases. The NMR parameters indicate enhanced intratumoral drug levels (tumor volumes did not increase between the two spectroscopic examinations). Elevated intratumoral 5-FU concentrations might be explained by a more efficient transfer of the drug from the vascular system into the stromal space, in accordance with the observation that NMR-detectable 5-FU is preferentially located in the stromal tissue (27). On the other hand, radiation therapy (28) as well as treatment with 5-FU (29) are known to increase tumor blood flow in experimental tumors. This effect is consistent with the data from our follow-up magnetic resonance imaging examinations of these patients, which indicate an increased uptake of Gd-DTPA in SCC after radiochemotherapy.4 An increase in tumor blood flow might also explain the enhanced intratumoral levels of FBAL, which is the dominant 5-FU catabolite in plasma (19). It is remarkable that 5-FU and FBAL were most frequently undetectable in large metastases (Tables 1 and 3). This finding can be explained by decreased vascular perfusion in these tumors, which leads to inadequate drug delivery.

In particular, in the largest tumor examined in this study, only DHFU was seen, i.e., appreciable amounts of this catabolic intermediate were produced during the 50-min infusion period even with 5-FU levels below the in vivo 19F-NMR detection limit. Unchanged concentrations of DHFU during radiochemotherapy (Fig. 5b) further support the conclusion that DHFU is produced in the tumor cells (the different behavior of the three resonances excludes an instrumental effect).

Another possible mechanism for the increase of 5-FU levels is reduced clearance of the drug from the tumor. This explanation would be in line with animal experiments which showed a prolonged retention of 5-FU after bolus administration in irradiated human colon adenocarcinoma in mice (9). Altogether, the mechanism that leads to the observed drug accumulation (Fig. 5a) in SCC of patients in the course of radiochemotherapy is still being examined in detail and different mechanisms must be considered.

In contrast to previous 19F-NMR studies of metastases in the human liver (13–15), the present study showed no correlation between intratumoral 5-FU levels (Iinf of 5-FU) and the response to treatment. One explanation is the different tumor type and therapy. In addition, only short-time follow-up data were available, and these showed in most patients of the study a partial response of the treated metastases. Changes of tumor sizes within a period of 3 months after treatment could be inappropriate for classification of response because examined tumors include not only vital tumor cells but also necrotic, inflammatory, and fibrotic tissue.

The lack of a correlation between 19F-NMR parameters and clinical response could be related to the ignorance of the treatment effect of carboplatin. Presently, this question cannot be resolved because treatment modalities using [5-FU+carboplatin]chemotherapy without irradiation or using 5-FU as single chemotherapeutic agent in combination with irradiation were not performed. It can be speculated that the suggested mechanisms for the alteration of intratumoral 5-FU pharmacokinetics during radiochemotherapy, resulting in an enhanced exposure of the tumor cells to the drug, may also be effective for the administered carboplatin. Recent animal experiments demonstrated the feasibility of platinum-195 NMR in vivo for monitoring local disposition kinetics of carboplatin in tissue (30). However, the sensitivity of this method is insufficient at present for monitoring platinum-containing compounds at clinically relevant concentrations. More sensitive techniques that could be adequate to this purpose are 1H-NMR (31), single-photon emission CT, or positron emission tomography; for example, Ginos et al. (32) obtained positron emission tomography scans using 13N-labeled cisplatin in patients with brain tumors undergoing chemotherapy with cisplatin.

In conclusion, the intratumoral 5-FU metabolism including the kinetics of 5-FU, DHFU, and FBAL could be monitored in vivo in this 19F-NMR study of SCC patients. The intermediate DHFU was seen in 90% of the examined patients with detectable metabolite signals and may be attributed to the metabolic activity of the tumor cells. Significant enhancements (more than 2-fold) of 5-FU and FBAL levels but no alteration of DHFU amounts in the metastases were observed during the second cycle of chemotherapy. The observation of increased drug levels within the tumor supports the notion of synergy of radiotherapy and 5-FU chemotherapy. This effect could be explained by an increased tumor blood flow related to radiation, chemotherapy, or both; but thus far, the mechanisms that are responsible for the accumulation of 5-FU in treated SCC are not definitive.

The ability of 19F-NMR spectroscopy to assess the pharmacokinetics of fluorine-containing drugs in tumors in vivo is unique and could be of use to optimize treatment protocols and to evaluate new radiation and drug dose schedules.

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Alterations of Intratumoral Pharmacokinetics of 5-Fluorouracil in Head and Neck Carcinoma during Simultaneous Radiochemotherapy

Heinz-Peter Schlemmer, Markus Becker, Peter Bachert, et al.


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