Experimental Study on the Carcinogenicity of the Cytostatic Drug Ftorafur (Tegafur)

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Long-term carcinogenicity of Ftorafur (Tegafur) was studied in rodents. Rats and mice were treated for one year per os with 40 (mouse) and 60 (rat) mg/kg Ftorafur twice a week and were followed for their entire life. Analysis of the data provide no evidence for the carcinogenicity of Ftorafur in rodents. These findings are similar to other antimetabolite studies and contrasts with the carcinogenic alkylating agents. (Pathology Oncology Research Vol 2, No 1–2, 69–70, 1996)

Key words: Ftorafur, Tegafur, carcinogenicity, mouse, rat

Introduction

Certain drugs used in cancer chemotherapy are carcinogens on the basis of animal experiments and epidemiological studies. Consequently, the risk of development of secondary cancer after successful chemotherapy is of growing importance. Therefore, clinical use of agents with minimal or zero carcinogenicity is desirable.

Ftorafur (FT) is an antitumor agent belonging to the antimetabolite family. FT is used to treat patients with breast cancer, including cases of tamoxifen- or adriamycin-resistance as well as cases of adjuvant and neoadjuvant chemotherapy of gastric and colorectal cancer. According to Japanese authors, the combination of uracil and Tegafur in a 4:1 molar ratio (UFT) has a greater antitumor activity than 5-fluorouracil and Tegafur in the case of liver cancer and nonsmall cell lung cancer. Furthermore, UFT was used for palliation as well. The aim of this study was to determine the carcinogenicity of FT in rodents.

Materials and methods

Ftorafur (Tegafur) (N1-2-tumoridyl-5-fluorouracil or 1-terahydrofuryl-2-5-fluorouracil) was purchased from V/O Medexporth (USSR). 176 young adult Wistar rats and 172 young adult C57Bl/ CBA mice (males and females) were kept in plastic cages under normal laboratory conditions and maintained on a conventional diet. Water was given ad libitum. The maximal tolerated dose for FT was 60 and 40 mg/kg in rats and mice, respectively.

Carcinogenicity in rats

Group N°1, 30 males and 30 females were given 60 mg/kg FT in 0.5 ml of a starch/water suspension per os twice a week for 12 months. Group N°2, 30 males and 30 females were given 0.5 ml of the starch/water suspension as above. Group N°3; 27 males and 29 females were left untreated.

Carcinogenicity in mice

Group N°1, 43 males and 52 females were given 40 mg/kg FT in 0.2 ml of a starch/water suspension per os twice weekly for 12 months. Group N°2, 39 males and 38 females were given starch/water suspension as above. Animals were observed for their entire lifetime. Necropsy was performed on all animals. Microscopic examinations of the following organs were performed: lung, spleen, liver, kidney, adrenal gland and any organs with tumors. Statistical evaluation: Student f-test

Results and discussion

Carcinogenicity of FT in rats

Benign and malignant tumors spontaneously occurred during the second half of life with equal frequency in vehicle treated and FT-treated animals (Table 1) which
Table 1. Effect of Flotrafur in rats

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Sex</th>
<th>No of animals with tumor (number)</th>
<th>% of animals with tumor</th>
<th>Benign tumor (number)</th>
<th>Malig. tumor (number)</th>
<th>Number of animals with tumor (&gt;1)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Flotrafur</td>
<td>male</td>
<td>29</td>
<td>6</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>n.s.</td>
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<td></td>
<td>female</td>
<td>26</td>
<td>1</td>
<td>1</td>
<td>0</td>
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<td>n.s.</td>
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<tr>
<td>Solvent</td>
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<td>8</td>
<td>3</td>
<td>7</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>female</td>
<td>25</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>0</td>
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<tr>
<td>None</td>
<td>male</td>
<td>27</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td></td>
<td>female</td>
<td>27</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>&lt;0.04</td>
</tr>
</tbody>
</table>

1. bronchial adenocarcinoma, intestinal adenocarcinoma, leydigoma, coecal hemangiendothelioma, seminoma
2. intestinal hemangiosarcoma, intestinal adenocarcinoma, abdominal hemangiosarcoma, pulmonary sarcomatosis, lymphoma
3. intestinal adenocarcinoma
4. lymphoma
5. skin fibroma & spinocellular carcinoma

was further supported by statistical analysis. Interestingly, a statistically significant difference in spontaneous tumor occurrence was found between the vehicle- and untreated groups (Table 1).

Carcinogenicity in mice

Benign and malignant tumors occurred mostly in females during the second half of life in both the FT-treated and control group (Table 2) without a statistically significant difference. The presented data provide evidence for the lack of carcinogenicity of FT in rodents. This is supported by the fact that spontaneous tumors remained low, they appeared in the second half of life and the majority of them were benign in FT-treated groups.

Carcinogenic cytostatic drugs belong mostly to the alkylating agents family: Cyclophosphamide, Chlorambucil, Myleran and Azacytidine. Interestingly, several antimetabolites were studied (6-MP, Methotrexate, 5-Fluorouracil) but none of them were found to be carcinogenic in experimental animals. This discrepancy may be explained by the fact that alkylating agents target DNA and are mutagenic, as well. The present experiment indicates that the antimetabolite, Flotrafur, can be used clinically without a major risk of development of secondary cancer.

Acknowledgement

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References


Table 2. Effect of Flotrafur in mice

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Sex</th>
<th>No of animals with tumor (number)</th>
<th>% of animals with tumor</th>
<th>Benign tumor (number)</th>
<th>Malig. tumor (number)</th>
<th>Number of animals with tumor (&gt;1)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flotrafur</td>
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<td>34</td>
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<td>0</td>
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<td>0</td>
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<tr>
<td></td>
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<td>0</td>
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<tr>
<td>Solvent</td>
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<td>32</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>female</td>
<td>29</td>
<td>6</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>&lt;0.34</td>
</tr>
</tbody>
</table>

1. lymphomas
2. lymphoma
3. skin lymphoma, lymphoma