A Potential Antitumor Factor (ATF) Isolated from a Bovine Bile Derivative (BBD)

Preliminary Report (III)

Henry S. PENN*, Hirotake KAKEHI, Noboru ARIMizu, M. ZEILER, and Hiromichi AKiba

Dept. of Radiology, School of Medicine, Univ. of Chiba

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The growth-inhibitory effect of the anti-tumor factor (ATF) on the Walker 256 carcinosarcoma, motivated trials of the compound in cancer-bearing patients.

Objective: A) To assess its affinity for cancer tissue, when combined with IHSA. B) To evaluate its antiproliferative effects during a "short-term" observation (6-8 weeks).

Findings: The pilot group consisted of seven patients, refractory to previous therapy. Whole-body scans, following the administration of the IHSA-ATF complex (500 μCi + 100 mg) showed positive, preferential concentration of the complex over tumor areas. Two patients died. One, (Ca. of breasts) two weeks after treatment was terminated; Response-negative. The other (Reticulum cell sarcoma) during therapy; Response-positive. (Measurable regression of axillary adenopathies, extensive vacuolation of tumor nuclei, indicating specific toxicity.) Complete autopsy report pending. The five remaining cases: Rhabdomyosarcoma and fibrosarcoma, the responses were negative. Squamous cell carcinoma, and hypernephroma, responses equivocal. Bronchogenic carcinoma, response-positive. Patient in "follow-up".

In a previous communication1) data were presented showing that the undialysable component obtained from a bovine bile derivative (BBD) inhibited the growth of the Walker 256 carcinosarcoma. The degree of inhibition was dose related. In the low dose treated group (1.25 mg/100 g-rat) tumor weights could not be differentiated from those of the controls. In the high dose treated group (10 mg/100 g-rat) most of the tumors regressed to milligram quantities or had undergone extensive necrosis. Histological examination of livers and kidneys of similarly treated controls showed no evidence of toxicity. In larger animals (dogs), the administration, ip of approximately 25 times the anticipated human dose, produced no change in the peripheral blood taken 1 hour and 24 hours post drug administration. These findings motivated further testing of the compound in man. Our human pilot study consisted of seven patients, who had been found refractory to other forms of therapy. They comprised a variety of inoperable malignancies in various stages of progression (Table 1).

Materials and Methods

Before treatment was instituted patients were given a "test" infusion, consisting of ATF 100 mg and IHSA 500 μCi, combined as

Fig. 1A (Case #IV)

Squamous cell carcinoma, ulcerating crater 8 cm × 12 cm, over left cervico-clavicular area.

* Present address: 2678 Glencower Ave., Los Angeles, Calif., U.S.A.
Table 1 Summary

"Short Term" response of seven patients to ATF therapy

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Hosp. No.</th>
<th>P. Sex. Age</th>
<th>Diagnosis</th>
<th>Duration &amp; total dose</th>
<th>Toxicity</th>
<th>Tumor response</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>13094</td>
<td>T.A. F. 49</td>
<td>Ca. of breasts</td>
<td>Two weeks ATF 1.5g</td>
<td>None</td>
<td>Neg.</td>
<td>Transitory pain alleviation</td>
</tr>
<tr>
<td>II</td>
<td>15643</td>
<td>T.M. M. 70</td>
<td>Bronchogenic Ca. rt. lung</td>
<td>Nov. 20-Jan.20 ATF 14g</td>
<td>None</td>
<td>Posit.</td>
<td>Objective excellent response</td>
</tr>
<tr>
<td>III</td>
<td>16078</td>
<td>K.T. M. 70</td>
<td>Rhabdomyo-sarcoma of neck</td>
<td>Dec. 12-70-Jan. 11-71 ATF 7.5g</td>
<td>None</td>
<td>Neg.</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>15825</td>
<td>T.Y. M. 40</td>
<td>Squam. cell carcinoma</td>
<td>Jan. 18-Feb. 19, ATF 10g</td>
<td>None</td>
<td>Equivocal</td>
<td>Surrounding tissue response approaches normalcy. Size of crater unchanged.</td>
</tr>
<tr>
<td>VI</td>
<td>14187</td>
<td>T.M. M. 51</td>
<td>Hypernephro-ma rt. kidney</td>
<td>Feb. 3-Feb. 10, ATF 5g</td>
<td>?</td>
<td>Equivocal</td>
<td>Complicated by obstructive jaundice. Pulmonary metastases, however, stabilized.</td>
</tr>
<tr>
<td>VII</td>
<td>14564</td>
<td>K.F. M. 23</td>
<td>Fibrosarcoma parotid gland</td>
<td>Feb. 3-Feb. 22, ATF 8g</td>
<td>None</td>
<td></td>
<td>Tumor has measurably increased in size. Treatment discontinued.</td>
</tr>
</tbody>
</table>

Fig. 1B Scan after the administration of the ATF-IHSA complex. (100mg+500μCi) four days later. (This patient did not receive Lugol's solution.)

previously described for BBD⁹. P. was given Lugol's solution 20 drops the night before, followed by 20 drops in A.M. and continued every morning for 2-3 days. Scans were made after 24 and 72 hours (Fig. 1A and B). Complete blood counts (CBC), plus total protein, BUN, SGOT, SGPT, alk. phosphatase, icteric index, bilirubin and electrolyte determinations were made. The blood counts were repeated at weekly intervals, other tests when indicated. Treatment consisted of diluting an equivalent of one gram sterile solution of ATF, prepared as previously described¹⁰, in 500ml Ringer's solution. This was administered iv every other day, thrice weekly for a period of 6-8 weeks.

Results and Discussion

As previously noted, all patients in this study proved refractory to other forms of treatment. The assessment of the clinical response, therefore, should be made in this context. Two of the seven patients died. One (case #1), diagnosed as "Carcinoma simplex", showed extensive involvement of the anterior chest including both breasts. Left shoulder and axilla manifested deep-seated necrosis. This patient received 1.5g of the medication (Nov. 11-26, '70). She expired 2 weeks after treatment was terminated. Objective response none. The other patient (case...
IV), (Ret, cell sarcoma) died after 2 weeks of therapy (Jan. 22-Feb. 7, '71). He presented a sublingual mass, complete nasopharyngeal obstruction, protruding bilateral axillary nodes and a palpable, firm, fixed abdominal mass extending to the left iliac crest. X-rays of chest showed bilateral pulmonary metastases. The response in this case may be considered positive, since the axillary nodes regressed measurably after 10 days of treatment. (Right axillary node regressed to less than 50%). Complete autopsy report pending. One patient (case #III, rhabdomyosarcoma of neck, with bilateral pulmonary metastases), showed no response after ten infusions, (Dec. 12-Jan. 11, '71) and treatment was discontinued. P. # VI: (hypernephroma of rt. kidney). After the 5th infusion (5g ATF) patient suddenly became acutely jaundiced. (van den Bergh's direct, positive, bilirubin 10.3, icteric index 40). Treatment was temporarily discontinued. Case # VII (Diagnosis fibrosarcoma). After 8 infusions (7.5g). This patient has shown no response to treatment. Facial tumor has increased measurably in size.

P. #III (Squamous cell carcinoma) presented an ulcerating crater over the left cervico-clavicular area, measuring 8cm × 12cm. The surrounding tissue was deeply cyanotic and indurated. The edges of the crater were covered by overhanging, thick, discolored skin, bleeding readily upon touch. Two papillary tumors were near the medial edge of the crater. After 10 infusions (10g ATF) the papillae sloughed off, leaving a necrotic base. The color and the consistency of the surrounding tissue is approaching normalcy. The dimensions and depth of the crater, however, is about the same. Response-equivocal.

P. # II (Bronchogenic carcinoma mid-lobe of rt. lung) P. H. Persistent cough in Jan. 1970 led to the diagnosis. Condition found inoperable. P. was given ²⁰Co 7940R up to Oct. 30, '70. Progression of the disease up to Nov. 20th is graphically shown in Fig. 2. P. I, patient has been bedridden for 3 months. Complains of intractable epigastric pain. A G.I. study revealed no abnormalities. During Nov. 20 to Jan. 20, '71 patient received 14g of ATF. During this period the pain had subsided and patient has been gaining weight. P. discharged to out-patient. He is up and around relatively symptom free. He is given 500mg ATF weekly as maintenance therapy (Fig. 2).

In presenting this admittedly limited study, both in terms of the number of patients and "short-term" observation, it should be emphasized, that our efforts were directed towards two objectives: first, to establish the potentiality of the ATF-IHSA, combination as a diagnostic procedure. The preferential concentration of the isotope over the tumor area, renders the test a safe diagnostic method (Fig. 2A and B). The second objective was to assess an initial response during a "short-term" observation to the ATF therapy. As previously mentioned our patients were refractory to all former treatments. The assessment, therefore, must be made in this context. If one were to design the "ideal" antineoplastic agent, he would, in all probability, endow it with the following cardinal attributes: A) high tumor-specific toxicity, B) a selective affinity for neoplastic tissue, C) absence of toxicity to any other tissue, or physiological system. A comparison of the hypothetical "ideal" with the naturally provided ATF discloses the presence of these elements in the compound. Extended trials may show that its antiproliferative action is effective on some tumors and not no others. On the basis of these findings ATF merits further use of the compound in a greater variety of malignancies and for a longer period of observation.
Conclusion
1) A new antitumor factor (ATF) is presented. 2) When combined with IHSA it concentrates preferentially in cancer areas. 3) It is devoid of toxicity in the doses employed.

Acknowledgment
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References
1) See accompanying paper