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Thio-tepa in advanced carcinoma

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THIO-TEPA IN ADVANCED CARCINOMA

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INTRODUCTION

With present knowledge, cancer can be arrested or completely eradicated only by surgery or radiotherapy. More and more investigations, however, indicate that chemotherapy may be an important means to alleviate discomfort, reduce length of hospitalization, increase survival time, and contribute to the possibility of cure by other means (1).

This thesis is aimed at discussing the use of one particular chemotherapeutic agent, Thio-TEPA. Its general usage will be described and its application in a series of cancer patients seen at the University of Nebraska Hospital and Tumor Clinic will be reviewed.

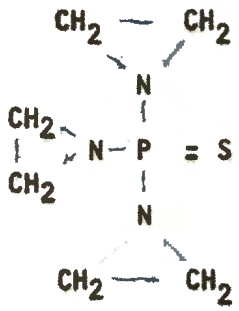
BIOCHEMISTRY

Thio-TEPA, or N, N^{1}, N^{11}-Triethylenethiophosphoramide, is a polyfunctioning alkylating agent related chemically and pharmacologically to nitrogen mustard and triethylene melamine (2). Thio-TEPA has also been known as TESPA and TSPA. It is not the same as TEPA (triethylenephosphoramide). Its mode of action is believed to be due to the release of ethylenimine radicals and their effect on actively dividing cells. It is for this reason that with the observance of a satisfactory palliative response it is necessary to continue medication on a maintenance basis.

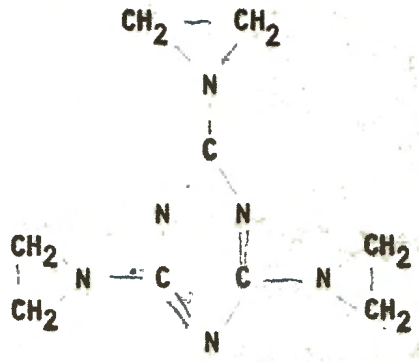
Among the real advantages of Thio-TEPA over nitrogen mustard are its greater margin of safety, fewer side effects such as nausea and vomiting, its greater selectivity, and ease of administration.

The following formulas reveal the similarity in chemical constituents of Thio-TEPA, nitrogen mustard (HN_2), and triethylene melamine (TEM).

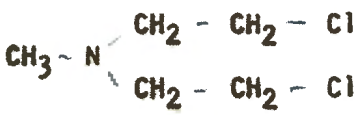
Thio-TEPA



Triethylene Melamine



Nitrogen Mustard



In the broad approach to cancer chemotherapy, neoplasia is defined as "a growth of cells which are largely or wholly independent of the organism that supplies their nutrition. They frequently possess an atypical structure, and they reach no definite limit of growth." (3)

A few generalizations about the chemical pattern of normal and neoplastic tissue include:

1. Normal tissue has an enzyme pattern which distinguishes it from any other tissue.

2. Tumors have qualitatively the same enzymes as normal tissues.

3. Enzymatic pattern of a tumor is largely independent of age and growth rate.

4. Tumors possess a more uniform and less diverse chemical pattern than normal tissues.

5. Neoplastic tissue undergoes reduction or loss of many of its functional activities.

6. Tumors do not stand outside the metabolic range of normal tissues.

7. Tumors tend to converge enzymatically to a common type of tissue.

Evidence has accumulated more and more to the effect that most of the change in neoplastic tissue is genetic and that DNA is the genetic material involved.

Hamilton (4) notes that "It has long been known as a result of classical studies in cytology and genetics that the chromosomes contain the genes which determine the character and rate of growth of cells. Chromosomes contain protein, desoxyribonucleic acid (DNA) and ribonucleic acid (RNA). DNA is probably responsible for the specificity of the hereditary material. Investigation has shown that the basic structure of DNA is the same in all cells, both cancer and normal."

According to Shapiro (5), low metabolite concentrations in malignant cells make them vulnerable to antagonistic chemotherapeutic agents of the antimetabolite class. Not every cell in any one tumor would be sensitive to a single drug. Shapiro has also found that as the enzyme concentration in tissue becomes lower, the degree of inhibition by the antagonist of the enzyme becomes greater.

In the case of Thio-TEPA, it is assumed that its activity is dependent upon its ethylenimine residues. There are three such residues in the composition of Thio-TEPA and TEM and one in HN_2. Hendry et al. (6) attribute the cytotoxic action of this drug to changes produced in the chromosomes and preferentially toward dividing cells.

The clinical application of triethylene melamine (TEM) by Karnofsky, Burchenal and associates in 1951 (7) actually opened the road to the preparation of other ethylenimine derivatives, including Thio-TEPA and a number of phosphoramides prepared by the research staff of the American Cyanamid Company.

EARLY EXPERIMENTATION

In one of the first articles concerning Thio-TEPA, Dr. Harry Shay and his Philadelphia group reported on the treatment of leukemia with triethylene thiophosphoramide (8). This group experimented with leukemias and inoperable non-leukemic lesions, using Thio-TEPA every other day intraperitoneally for nine days in leukemic rats as an initial experiment. The first and second doses were 3 mg. per Kg. of body weight. Peripheral blood counts that ranged from 50,000 to 300,000

returned to normal levels of 10,000 or less within six days.

Shay also found that while Thio-TEPA differed from TEPA only in the replacement of a double-bond oxygen atom in the molecule by a sulfur atom, this difference accounted for many more beneficial effects in the treatment of patients with chronic leukemia. In his six-month study (8) of 49 patients treated with Thio-TEPA, 39 of whom had malignancies of the hematopoietic system and 10 of whom had inoperable malignant lesions, Shay concluded that the drug did have a suppressive effect in chronic leukemias but not in acute leukemias. He also noted that since Thio-TEPA was only suppressive and not a cure, possible resistance to the drug might develop in the malignant cell after prolonged therapy.

Thio-TEPA has been tried with varying results in the palliation of a large variety of neoplasms. More consistent results have been seen in adenocarcinoma of the breast and ovary, lymphoma and melanotic sarcoma. The following neoplastic diseases have also been reported to respond fairly consistently to the drug (9): polycythemia vera, Hodgkin's disease, and chronic lymphatic and myelogenous leukemia. Those diseases showing occasional response to Thio-TEPA include carcinoma of lung, bronchus, colon and rectum, pancreas, thyroid, salivary gland, stomach, bladder, kidney, male genitalia, and uterus; Wilms's tumor, and glioblastoma. Many authors would argue the validity of beneficial results in many of the above-named disease entities.

MODE OF ADMINISTRATION

One of the strong points in favor of using Thio-TEPA is its ease

of administration and availability of routes of administration. It may be placed in any of the body cavities after paracentesis; i.e. intrapleural, intraperitoneal, intrapericardial. However, repeated injections may be necessary to insure action on tumor implants, since Thio-TEPA is probably effective only on active cells.

Thio-TEPA may also be given locally into the tumor mass. There is usually little local reaction or pain. The drug has a pH of 7.8 to 8.0 and is compatible with procaine hydrochloride or epinephrine hydrochloride.

Parenteral administration may be either intramuscular, intravenous, or intra-arterial. A suggested dosage schedule is .2 mg. per Kg. for 5 days, for a total of 1 mg. per Kg., and thereafter a maintenance of .2 mg. per Kg. weekly based on weekly blood counts (10). The dosage of Thio-TEPA must be carefully individualized. In successfully treated cases on prolonged maintenance therapy, over 1500 mg. (mean of 25 to 300 mg.) has been given and may be done as long as the patient shows a response and does not exhibit hematopoietic disturbances.

It has also been established that Thio-TEPA is radiomimetic and is strongly inhibitory to the hematopoietic system. Bone marrow depression is difficult to predict and may appear 5 to 30 days after treatment. The white blood count and platelets are the best indices of depression. When the WBC has fallen to 4,000 and/or the platelets to 150,000 or less, therapy should be discontinued. There is no correlation between hematopoietic depression and tumor regression. It has been observed that a

greater effect may be obtained when radiation is or has been given. Death has been reported from septicemia and hemorrhage as a direct result of hematopoietic depression. In the presence of infection, this drug should be administered with caution. If the WBC falls below 3,000 appropriate antibiotic therapy should be begun.

REVIEW OF CASES OF DR. BATEMAN

One of the most avid proponents of Thio-TEPA has been Dr. Jeanne Bateman, who has put the drug to use in many cases of far advanced malignancies. In 1956, in the Journal of the American Medical Association, she reports on the use of phosphoramide drugs in the treatment of 122 patients with mammary cancer (11). Treatment ranged from one to 24 months. The youngest patient was 26 years old, the oldest 85. Thirty-eight individuals were in the fifth decade of life. The interval between diagnosis and institution of chemotherapy ranged from one to 14 years. Surgery included biopsy only in 22 patients and mastectomy in 100 patients. Many of these patients were additionally treated by radiation, hormone therapy, adrenalectomy, radio-active gold, TEM, nitrogen mustard, and propylthiouracil.

Thio-TEPA was given in water solution with 10 mg. of the drug per cc. TEPA was employed in 20 mg. per cc. dosage. (See Table I.) Total dose with Thio-TEPA ranged from 15 to 1145 mg. for a period of one to 103 weeks. The average dose was 336 mg., average duration of time 22 weeks. TEPA dosage was 5 to 430 mg. for one to 37 weeks, average

total dose being 139 mg. for a duration of 7 weeks on the average.

Table I. Dose Levels in Phosphoramide Therapy in 122 Patients with Mammary Carcinoma. (11)

Route Employed	Dose Level, mg/Kg. Thio-TEPA	TEPA	Dose Interval, Wks.
IV	5-30	5-40	1-4
Intrapleural	10-40	15-60	1-4
Intraperiton-eal	10-40	...	1-4
Intrapericar-dial	20-25	30	Occasional
Intratumor	3-50	3-80	1-4
Intramuscular	10-20	...	1-4
Oral	5-10	10-20	1-7 days

Dr. Bateman notes that "Subjective improvement of some degree occurred in the majority of cases ... There was improvement in appetite, weight gain, control of dyspnea, cough, pain, and pruritus." Eighty-one persons manifested some type of objective improvement for periods of one to 21 months, while 41 (or 34%) showed no objective response. Duration of improvement averaged 5.4 months in the group of patients who died or were lost to follow-up, and 8.3 months in the living patients examined. Dr. Bateman does admit that progression and regression of different lesions can take place simultaneously in the same patient, making evaluation difficult.

In her study, healing of ulceration and partial-to-complete regression of primary tumors and metastatic nodes were observed in two-thirds of patients. Facial edema, she reports, secondary to large neck nodes, completely disappeared in 3 patients. Decrease in size of pulmonary metastases was observed in 5 of 11 patients. Three of 5 patients showed relief of central nervous system symptoms, i.e. ataxia, visual disturbances, etc.

"Control of accumulation of serous cavity fluid by local injection of phosphoramide after withdrawal of fluid was achieved in two-thirds of cases so treated." In 26 of 36 patients with pleural fluid, no further taps were required for periods of one to 21 months after one or more intrapleural injections of drug (11).

Hematopoietic depression was the one serious side effect. Dr. Bateman feels that the WBC was a good guide in determining dosage. She also states that "the only agents that appeared to aid significantly in protecting the hematopoietic system from the depressant effects of phosphoramide drugs were the adrenal cortical hormones." Her final statement was: "The phosphoramide drugs are useful agents in the prolonged palliation of advanced mammary carcinoma."

Furthering her studies of Thio-TEPA, Dr. Bateman reports on 96 patients treated for advanced ovarian carcinoma (12). Treatment ranged from one to 61 months. Thio-TEPA was administered at the time of surgery in 16 patients, post-operatively in 28 patients, and for recurrence in 52 patients. Local injection into tumor was achieved whenever possible.

There was control of pleural effusion in 11 cases, control of ascites in 10 cases, and regression of tumor in 23 cases. Subjectively, many had lessened pain and an increase in well-being. Thirty-one patients were still living at the time of publication. Sixty-five had died or were lost to follow-up.

Survival time, in this study, from the date of demonstrable metastases was 94.8% at 3 months, 85.4% at 6 months, 83% at 1 year, 31.5% at 3 years, and 31% at 5 years.

At an exhibit which I personally viewed in Miami Beach at the American Medical Association Convention last June, Dr. Bateman listed these qualifications which would be desirable for an anti-cancer agent:

1. Anti-tumor effectiveness
2. Long action
3. Minimal or absent clinical toxicity
4. Ready solubility
5. Adaptability to many routes of administration
6. Predictable hematologic effect
7. Toleration by host for indefinite periods

Among Dr. Bateman's indications for chemotherapy were:

1. Wound and blood sterilizing agent (one dose or short course for early, non-metastasizing lesions).
2. Post-operative course or maintenance chemotherapy for tumor which has metastasized or is advanced locally (blood vessel or lymphatic invasion), but in which all gross neoplastic tissue was removed.

3. "Inoperable" cases treated by limited surgery and maintenance chemotherapy.

4. Maintenance chemotherapy for:

   a. Advanced residual disease following other therapy, as partial resections, etc.

   b. Advanced recurrent disease.

   c. Untreated inoperable disease.

In evaluating some 1066 cases over a period of six years, Dr. Bateman listed the following responses in some cases:

Subjective

Improvement in well-being

Increased appetite

Control of dyspnea, cough, and dysphagia

Control of pain and muscle spasm

Objective

Regression of tumor masses and metastatic nodes

Regression of edema secondary to obstructive tumor

Control of serous cavity effusion (pleural, pericardial, ascitic)

Healing ulcerating lesions

Regression of nodules from pulmonary metastases

Regression of hepatic involvement

Regression of signs of CNS toxicity

Recalcification of osteolytic bone lesions

Side Effects

Occasional pain or discomfort following local injection

Rare and questionable nausea

Hematopoietic depression, reversible by slowing therapy

Leukopenia preceding other effects

Thrombocytopenia

Mild RBC depression

According to Dr. Bateman, hematopoietic depression regulated by weekly blood counts and maintenance of WBC at 2000-3000 cells must be followed. She also noted that in the presence of renal impairment, dosage of the drug should be reduced because the "mustard drugs" are excreted chiefly through the kidney. Dr. Bateman recommends small maintenance doses of adrenocortical drugs as a protective mechanism for the hematopoietic system, as well as to improve appetite and sense of well-being. Drug action, she concludes, is slow and results usually become apparent over many weeks' duration.

REVIEW OF CASES BY OTHER WORKERS

In a communication by Ultmann, Hyman, et al. in 1957, 100 cases were studied over a five-year period (13). Method of drug assay by this group was as follows: "Thio-TEPA, a dry, crystalline powder, was dissolved in sterile isotonic chloride solution to make a final concentration of 10 mg. per ml. The solution was passed through a Seitz filter and tested for sterility by routine bacteriologic methods. The Thio-TEPA was then stored in sterile rubber-capped vials at 2 degrees

Centigrade for a maximum period of six weeks."

In this study, the authors, noting the difficulty in evaluating subjective responses, listed only objective responses such as definite decreases in tumor masses. In the 100 cases, there was measurable improvement in only 32 patients, and in only 7 was improvement striking. Remissions of three months or longer were obtained in only 10 patients. Hodgkin's disease, reticulum sarcoma, and ovarian carcinoma were the only tumors among those studied that showed any noticeable clinical response to the drug.

Shay and Sun (14) reported in 1955 on 47 patients with inoperable metastatic cancers. The results were as follows:

1. Carcinoma of the breast: Of 12 patients treated with Thio-TEPA, 6 showed objective improvement of regression of enlarged nodes and tumor nodules that continued for 2 to 12 months; 4 showed no definite improvement; the remaining 2 did not receive enough Thio-TEPA to evaluate results. Of the 6 patients showing objective improvement from Thio-TEPA, 3 who had shown no beneficial effect with combined roentgen ray, testosterone, and/or castration therapy, responded well for 12, 7, and 4 months respectively.

2. Carcinoma of the ovary: Of these patients, 3 of whom were treated with the drug, 2 obtained temporary improvement in that reaccumulation of abdominal fluid was prevented and some regression in the size of the abdominal mass was produced. Thio-TEPA was later discontinued because of failure of continued improvement.

3. Malignant melanoma: Two patients showed temporary regression

of the tumor mass, but the disease progressed rapidly.

4. Other inoperable cancers: Patients with carcinoma of the lung, larynx, esophagus, stomach, colon, sigmoid, rectum, small intestine, prostate, thyroid, and biliary tract showed none or only slight improvement.

Shay went further to elicit the toxic effects of Thio-TEPA: "ThiosTEPA can be administered by any route with little or no effects. There was no immediate systemic reaction, such as nausea, vomiting or anorexia. Pre-treatment and follow-up studies of renal, phenothalein excretion and concentration tests, and complete liver function profiles, including serum bilirubin, cephalin-flocculation, colloidal gold, thymol turbidity, gamma globulin, serum cholesterol and esters, phospholipids, neutral fats and total lipids, serum alkaline phosphatase, and BSP tests showed no changes during Thio-TEPA therapy." Bone marrow depression constituted the most serious side effect encountered. Dr. Shay concluded his study on this note: "Improvement produced by Thio-TEPA is of course limited, and lesions that respond at first sooner or later become resistant, and new metastases may develop in spite of continued treatment."

Thirty-four cases of breast cancer at various stages were treated with either Thio-TEPA alone or Thio-TEPA with testosterone in a series of cases reviewed by Watson and Turner (15). The intramuscular route was used in all patients. In the 11 patients who received Thio-TEPA alone, 15 mg. of the drug was given two or three times a week until the WBC fell below 3,000 cells per cubic millimeter. In the remaining 23 patients who

received testosterone in combination with Thio-TEPA, the individual dose of Thio-TEPA was eventually increased to 30 mg. on alternate days until a total dose of between 180 and 300 mg. was given. Testosterone propri-onate was administered by intramuscular injection, 200 mg. five times a week, beginning one week before Thio-TEPA and continuing 2 weeks after.

In this series, it was noted that certain sites, principally skin and primary tumors, responded earlier than others. Regression of tumor growth was obtained in 8 out of 11 patients treated with Thio-TEPA alone, and in 22 out of 23 patients receiving Thio-TEPA and testosterone. Four patients failed to show any response and died within four weeks of com-mencing therapy. Four others died after a period in which the progress of the disease was arrested. Those patients who showed regression of the tumor growth experienced marked subjective improvement in sense of well-being.

Eleven patients had metastatic bony lesions; 8 responded to Thio-TEPA and discontinued pain-relieving pills. Urine calcium output and serum alkaline phosphatase levels also dropped.

Nine patients with metastases to lung, liver, and abdominal cavity were treated. Four patients showed no response. In the remaining, ar-rest of the progress of the lesions and regression in size occurred for $2\frac{1}{2}$ to 12 months. Where pleural and peritoneal effusions were encounter-ed, inhibition of their formation was obtained. Lung secondary tumors responded as a whole better than liver secondaries.

The changes found in breast tumors appeared to be related to the total amount of Thio-TEPA administered and the duration of treatment

prior to mastectomy. The tumors felt much softer; and histologically after 6 months of treatment, several revealed dense fibrous tissue replacing tumor cells. Cells in mitosis in some cases showed clumping and fragmentation of the chromosomes, according to these authors.

In a more recent study (16), a comparison between nitrogen mustard, an old standard form of therapy, and Thio-TEPA, the relatively newer drug, was undertaken. The interesting note to this study was that it was one of the first large-scale collaborative efforts, pursued by a group of workers in nearby medical centers. The object was to provide a technique for study of a larger number of patients than could be seen in one hospital, to express the effect of the drug on the tumor quantitatively, and to give the drug to groups of patients with comparable extent of disease. In essence, then, this was one of the initial experiments set up in order to provide a protocol of criteria for large-scale study of chemotherapeutic agents.

The drug was injected once daily for 4 days at the start of the treatment, followed by a series of weekly injections starting 2 weeks after the first course of injections, unless hematopoietic depression occurred. The individual doses were .1 mg. per Kg. for nitrogen mustard and .2 mg. per Kg. for Thio-TEPA. The full course of treatment was 90 days.

Two-hundred and fifty-eight patients were studied. Two study groups were formed, in comparing the two drugs. The two treatment groups had approximately equally extensive disease.

In those treated with nitrogen mustard, 8 out of 9 Hodgkin's disease patients had marked regression of tumor, while this was true in 7 of 11 treated with Thio-TEPA. The mean remission following Thio-TEPA was 44±7.3 days, while that achieved on nitrogen mustard was 81±5.6 days. The mean maximum reduction in tumor size was 36±6 % for patients on Thio-TEPA, and 70±6% for those on nitrogen mustard. Both of these differences, according to the authors, were significant at the .01 level.

Concerning cancer of the lung without prior irradiation, "More patients receiving nitrogen mustard had anti-tumor effect than those receiving Thio-TEPA." The mean duration of tumor regression was 65±19.0 days in 4 patients responding to Thio-TEPA, and 50±8.5 days in 12 patients responding to nitrogen mustard. Neither of these differences was significant at the .05 level, according to the authors.

In those patients with carcinoma of the lung with prior irradiation, there were few anti-tumor effects and no significant differences between the two drugs. This group of patients was treated 6 months after diagnosis while the patients who had received no irradiation were treated 1.5 months after diagnosis.

The malignant melanoma group showed no significant differences, although two patients on Thio-TEPA showed a transient anti-tumor effect.

In cancer of the breast, both drugs were effective. The mean length of regression was 45±11.6 days for 4 patients responding to Thio-TEPA, and 36±7.5 days for 9 patients responding to nitrogen mustard. The mean reduction in tumor size was 30±19% for Thio-TEPA, and 44±9% for mustard. The differences were not significant at the .05 level.

The authors concluded that, "There were no significant differences for any of the diseases between the survival of patients receiving nitrogen mustard and those on Thio-TEPA." Nor did the authors find any striking differences in hematologic or toxic effects, as is pointed out in the following chart:

LIST OF MAJOR UNTOWARD EFFECTS AS DETERMINED BY PATIENT VOTING (16)

Type of toxicity	Patients on HN_2	Patients on Thio-TEPA
Excessive vomiting	2	0
Thrombocytopenia and leukopenia without sepsis	5	2
Thrombocytopenia and leukopenia with sepsis	0	3
Mental confusion	1	0
Totals	8	5
Total Patients	122	121

Gumport et al. (17) in 1958 reported 18 cases of advanced malignant melanoma which were treated by radiation without success. Thio-TEPA was used in 16 cases after which biopsies were taken. The initial dose was usually 40 mg. in or near the site of the tumor. Then 5 to 20 mg. were given every week until regression or toxicity resulted. Fourteen cases received adequate observation. Two were still alive at time of publication, while 12 had died. Of the 16 cases, 5 obtained marked benefit, one stayed approximately the same, 8 showed no effect, and 2 patients were not observed sufficiently. In those patients improved, a few weeks to a few months was the usual remission.

J. C. Wright et al. (18), after effectively inhibiting metastases in rat mammary carcinoma, studied the results of Thio-TEPA treatment in 94 human cases. Rate of administration was 10-20 mg. per week. Improvement, they noted, usually occurred between 7 and 13 days, but in some cases was as long as 95 days. Fifty-nine of 94 patients had a depression in WBC of less than 5,000 at least once. The authors noted objective improvement in 5 out of 17 cases of carcinoma of the breast, 5 out of 16 cases of malignant melanoma, 2 out of 5 cases of carcinoma of the ovary, none out of 9 cases of carcinoma of the bowel and rectum, 3 out of 5 cases of Hodgkin's disease, and none out of 4 cases of carcinoma of the lung. From these results, they concluded that breast and ovarian carcinoma and some malignant melanomas improved, as well as some lymphomas, but little was gained in the treatment of bowel, rectum or lung cancers.

G. E. Moore (19) used a 50% reduction in size of nodules for one month as the basis for objective response and noted 9 out of 25 cases of cancer of the breast to give objective remission. Remissions lasted one to 3 months; in those subsequently treated with a second dose, 6 out of 10 showed another remission.

USAGE IN PREVENTING DISSEMINATION OF TUMOR CELLS AT TIME OF SURGERY

In the past few years, surgeons have become more interested in chemotherapy. Most of their work has been directed towards preventing dissemination of tumor cells into the wound, venous system, and lymphatics. In current experimental and clinical studies the drugs that are most used are such cytotoxic agents as nitrogen mustard, Thio-TEPA,

phenylalamine mustard, and CHlorpactin XCB (20). Among the various means of administration are local application in the wound, intravenous usage, and arterial perfusion, employing the extracorporeal pump oxygenator. The advantage of the perfusion technique lies in the fact that large doses of a drug may be administered to an isolated part of the body, such as any extremity, without entering the systemic circulation, so that the bone marrow is protected.

Dr. Warren Cole and his group (21), postulating that tumor cells might be disseminated by operation, undertook a study in 1957 using anti-cancer drugs in a prophylactic way.

Cellular suspensions from Walker rat 256 carcinosarcoma were injected into the portal vein, peritoneal cavity, or systemic vein. One series of animals was injected with 110,000 cells, whereas another series was injected with 220,000 cells in an effort to determine whether the anticancer agent would be more effective against the smaller dose of cancer cells.

The experiments indicated, according to the authors, that Thio-TEPA was slightly more efficacious in the prevention of "takes" in rats with the Walker 256 carcinosarcoma than was nitrogen mustard. Both drugs were found to be less effective when the larger injection of cells was given (220,000 cells).

In a smaller group of animals, Cole and associates (21) found that nitrogen mustard did not decrease the "takes" in the liver when it was given 48 hours after injection of cancer cells into the portal vein. They thus theorized that if these results were valid, the maximum safe

dose of anticancer drug should be given at the time of operation in order to destroy or subdue the growth of microscopic nests of cells which might give rise to metastases.

APPLICATION IN SO-CALLED "HOPELESS CASES"

Thio-TEPA and its analogues have found considerable application in patients with so-called "hopeless" carcinoma in whom all curative measures had failed. Schell and Hall (22) in 1958 tried TEM and Thio-TEPA in 40 such patients.

The authors point out that there were "some successes and some failures" but that in many cases there was a great "psychological lift" by offering a form of treatment where all others had failed.

Thio-TEPA was given in 10-20 mg. per cc. doses by IM routes, into serous cavities, and directly into tumor masses. TEM was given orally (2-5 mg.) and into serous cavities. Injection into tumor masses was avoided because of massive necrosis of tumor tissue.

The following cases and results are recorded:

HEAD AND NECK: Three patients with squamous cell carcinoma were treated by local or systemic therapy with Thio-TEPA, intrapleural installation of TEM, or both. In one case of recurrent carcinoma of the parotid involving orbit, base of skull, maxilla and hard palate, treatment was by two injections of Thio-TEPA of 80 and 100 mg. respectively. "Moderate diminution in size of mass was observed and marked relief of pain occurred which continued until the patient's death two months later of apparent airway obstruction." One patient with anaplastic adenocarcinoma of the thyroid was subjectively benefited by IV Thio-TEPA 10 mg. every other day for 8 days with improvement in breathing but not in

size or rate of tumor growth.

BREAST: Five patients were treated and the most prolonged good results were obtained in this disease. Paradoxically, the intrapleural use of either Thio-TEPA or TEM was uniformly unsuccessful in controlling pleural effusions due to metastases. Good response was gained by local injection of Thio-TEPA into recurrent masses.

CHEST AND ESOPHAGUS: No palliation in two cases treated by IV Thio-TEPA.

GASTRO-INTESTINAL TRACT: Seven cases of adenocarcinoma of the stomach and intestinal tract were treated. Instillation of TEM intraperitoneally relieved ascites in 3 cases, obviating further paracenteses. Three patients were treated by IV or intratumor doses of Thio-TEPA without objective relief, although one patient with obstructive adenocarcinoma of the sigmoid experienced temporary relief of diarrhea and pain. In another instance, "The palliation obtained in a case of adenocarcinoma of the jejunum was of an unusual nature insofar as the primary problem was recurrence in an upper midline surgical scar, with severe pain apparently secondary to involvement of the periosteum and perichondrium of the costal arch. Three local injections of Thio-TEPA of 30-40 mg. each produced, in the patient's words, '90% relief of pain' and palpable softening and regression of tumor."

FEMALE INTERNAL GENITALIA: "The response of ovarian tumors to these agents is often gratifying, especially serous cystadenocarcinomas." Either TEM was instilled into the peritoneal or pleural cavity

followed by oral dosage, or Thio-TEPA was injected directly into tumor masses. By transrectal or transvaginal injection into tumor masses, two palliative colostomies were averted with satisfactory control of tumor growth until death intervened from some cause other than intestinal obstruction. Response of endometrial cancer was not as dramatic as that seen in ovarian tumors; nevertheless, marked diminution in vaginal hemorrhage occurred in one case. In another, lymphedema of the legs subsided, and in a third, relief of partial bowel obstruction was obtained.

SKIN AND EXTREMITIES: Three patients with malignant melanoma showed no response to IV Thio-TEPA; in one case, some improvement followed direct injection into subcutaneous nodules.

ORIGINAL STUDY

The clinical cancer chemotherapist is beset with problems that make controlled studies difficult, which Dr. Daniel Miller and his group found to be true, as did the present writer in evaluating the results on University of Nebraska Hospital and Outpatient Clinic patients.

The drug must always be used as part of the total care of the patient. It is, of course, impossible to use untreated controls as is possible with animal studies. Further, the coexistence of disorders such as hypertension, renal disease and liver disease may influence the results. Final evaluation must, then, be based on the growth of the primary tumor or metastases as well as marked improvement in the patient's health and prolongation of life.

In the series of patients studied at the University of Nebraska

College of Medicine, 71 cases were seen between 1956 and 1960, either in the Tumor Clinic or during hospitalization at University Hospital. Thio-TEPA was given, under the direction of Dr. Daniel Miller, in varying doses and over variable periods of time. Hematologic responses governed injection intervals so that dosage varied with leukocyte and platelet counts (23).

Most of these patients presented with far-advanced malignancies. All available routes of injection were employed, i.e. intravenous, intramuscular, intrapleural, intraperitoneal and intratumor, so that different routes could be evaluated as to effectiveness.

Many in our group had been previously treated by roentgen therapy, hormonal therapy, surgery, and other forms of chemotherapy such as TEM and nitrogen mustard. This made evaluation particularly difficult, since results might be due to therapy other than Thio-TEPA. We do contend, however, that this drawback is met with in most forms of scientific work evaluating a new agent.

Moreover, we did attempt to record accurately the subjective and objective responses, total drug dosage, and time interval between the injections.

Diseases studied included: carcinoma of the breast, ovary, lung, tongue, esophagus, stomach, colon and rectum, pancreas; malignant melanoma; carcinoma of the endometrium and cervix; squamous cell carcinoma of the skin and maxillary sinus; basal cell carcinoma of skin and appendages; liposarcoma and sarcoma; and teratocarcinoma of the testis.

Breakdown of cases was as follows:

1. Miscellaneous tumors, 7 (which included teratocarcinoma, liposarcoma, metastatic carcinoma with primary unknown, sarcoma, squamous cell carcinoma of the cervix and adenocarcinoma of the endometrium).

2. Carcinoma of the stomach, 6.

3. Carcinoma of the breast, 4.

4. Carcinoma of the ovary, 5.

5. Carcinoma of the lung, 15.

6. Carcinoma of the esophagus, 3.

7. Malignant melanoma, 3.

8. Carcinoma of the pancreas, 4.

9. Carcinoma of the colon, 11.

10. Carcinoma of the skin, 13 (which includes basal and squamous cell carcinoma of ear, eyelid, maxillary sinus, tongue, soft palate, and face).

In the 15 cases of carcinoma of the lung, dosage levels varied from 30 mg. to 310 mg. with an average dose of 110 mg. Routes utilized were intravenous and intrapleural. Age ranges of patients were from 39 to 75, with an average age of 58.7 years.

Six patients received no relief from Thio-TEPA either subjectively or objectively. One patient could not be evaluated. Of the 8 who improved on Thio-TEPA, one noted subjective relief in being able to breathe more easily. He also gained weight and was in better spirits. However, x-ray of the lungs revealed that the disease process was unabated, and

the patient died 7 months later. One patient died 3 months after beginning Thio-TEPA. For 2 of the 3 months he was able to eat well and had less chest pain and cough. In one patient treatment covered almost a year. During this time, he was noted to have subjective relief for brief periods of time, i.e. less cough, hemoptysis, an increased appetite, and less chest pain. Extension of his disease, however, as proved on x-ray, did continue and the patient died one year later. Total dose of Thio-TEPA was 310 mg. Another patient was treated for 6 months with both Thio-TEPA and radiation therapy. He was noted to have less pain and hemoptysis, but no decrease in size of mass by x-ray. He died 8 months later. Over a 1½-year period of time and on a dosage of 220 mg. of Thio-TEPA, one female patient experienced less cough, hemoptysis and chest pain. She maintained her weight well and no blood count depression occurred. She had received radiation therapy prior to Thio-TEPA. One of those who improved died 10 months after receiving Thio-TEPA and x-ray concurrently. He obtained brief relief of cough, hemoptysis, and chest pain; but pleural effusion continued and subcutaneous nodules eventually developed on the chest wall. One patient had a marked anemia due to previous heavy irradiation, but did experience relief of shortness of breath before expiring 6 months later. The last patient in the lung series had received previous courses of nitrogen mustard therapy and a lobectomy some 2 years earlier. He had less cough, chest pain, and hemoptysis and felt well for some 6 months on Thio-TEPA. Some blood count depression was noted in this patient. He died 3 months later, but lived for nearly 3 years after lobectomy, nitrogen mustard and Thio-TEPA therapy.

Six patients with carcinoma of the stomach were studied. Dosage ranged from 30 to 225 mg., with an average dose of 110 mg. Routes employed were intravenous, intramuscular, intraperitoneal, and into gastric and liver nodules. Ages were from 41 to 78, with an average age of 56.3 years. Five patients showed little-to-no improvement on the drug. One of these showed no response to 30 mg. of Thio-TEPA injected into gastric and liver nodules. Another one of the 5 would feel better for a few days following peritoneal tap and installation of Thio-TEPA but went rapidly downhill. One patient died 5 months after Thio-TEPA was instituted. Although his ascites and pain were less for 3 weeks following intraperitoneal Thio-TEPA, he lost weight rapidly, noted recurrence of pain, and experienced metastases to his spine. All in this group did have extensive metastatic disease by the time Thio-TEPA was instituted.

Eleven of the 71 patients had carcinoma in some portion of the colon or rectum. Dosage levels were from 25 to 205 mg., with an average dose of 91 mg. Routes employed were intravenous, intramuscular, intraperitoneal, and into liver metastases at time of surgery. Ages ranged from 42 to 76, with an average age of 65.3 years. One patient showed no relief, while we were unable to evaluate one other patient. One woman showed symptomatic improvement after one course of Thio-TEPA but continued to lose weight. She was last heard from in June of 1959, still living, one year after this single dose. Another lady improved for 4 months on Thio-TEPA. Her disease process was adenocarcinoma of the colon with metastases to the broad ligament. Following radiation therapy

in 1954 and pelvic resection in 1956, she was free of pain until 1957. After Thio-TEPA, she looked and felt better and could discontinue her pain pills for 4 months. One interesting case was a lady with adenocarcinoma of the hepatic flexure. After an ileo-transverse colostomy and 25 mg. of Thio-TEPA, she said she would not return but would leave the rest up to the "Lord." In a letter received 5 months later, she remarked that she felt well and was having no bowel difficulties. In another patient, 135 mg. of the drug was given over a 3-month period. He subsequently died, and at autopsy the tumor seen several months before at surgery had decreased to about one-half the former size. One lady had undergone extensive surgery in December of 1958 for carcinoma of the colon. She began on Thio-TEPA therapy in April of 1959, noting much improvement symptomatically and being again able to carry out her functions. Liver nodules and ascites remained constant, however, as of 8 months later. She had received 205 mg. of the drug by intravenous, intramuscular, and intraperitoneal routes. One lady felt better for only 4 days after Thio-TEPA (57 mg.), and died 5 months later with extensive masses in the pelvis and extreme pain. She had adenocarcinoma of the recto-sigmoid colon with liver metastases. A 71-year-old female had 70 mg. IV and into liver metastases at time of surgery. Six months later she was getting along well under the care of her local physician with normal eliminations. She was subsequently lost to follow-up. One patient had less pain only after 120 mg. of Thio-TEPA but died 6 months later with metastatic disease. Finally, a 76-year-old male had good

symptomatic relief and improvement in sense of well-being on 180 mg. of the drug for 5 months. He underwent surgery 3 months before Thio-TEPA was started for adenocarcinoma of the rectum and transverse colon. The unoperated rectal mass remained the same, and progression of lung metastases was noted and the patient died in October of 1960.

We were able to fully evaluate only 5 cases of carcinoma of the ovary. Dosage levels in this group ranged from 20 mg. to 120 mg., with an average dose of 68 mg. Routes employed were intramuscular and intravenous. The age span in this group was 46 to 77, with an average age of 63 years. One 75-year-old patient with adenocarcinoma of the ovary and metastases to omentum noted improvement in strength, appetite and relief of partial bowel obstruction. She was also able to return to her housework. In addition, tumor implants were no longer palpable on pelvic examination. Total dosage was 120 mg., given IM and IV. She was later lost to follow-up. Another 71-year-old housewife had cystadenocarcinoma of ovary with ascites and gastrointestinal involvement. She died 5 weeks after Thio-TEPA, but felt better during this interval. No objective response was seen, however, as noted by generalized metastases on x-ray. Three other patients with extensive metastatic disease failed to show any improvement.

Unfortunately, our series includes only 4 cases of carcinoma of the breast. This was in large part due to conflict with another study, The National Adjuvant Chemotherapy Program. Thus, breast patients were given either placebo or Thio-TEPA in secretly-coded vials. We were not

given the opportunity to decipher the code or interpret these results. Hence, 4 cases only received strictly Thio-TEPA. Dosage ranged from 60 to 150 mg. with an average of 75 mg. Routes were intravenous and intrapleural. Ages of patients were from 39 to 86, with an average age of 47.6 years. One 91-year-old female demonstrated remarkable results. She first had a radical mastectomy in 1941 for carcinoma of the breast. At age 86, recurrence in the skin of the chest wall was observed. At the age of 88, she received 150 mg. of Thio-TEPA over a 5-month period; during this time, pain decreased, bleeding from the chest wall abated, edema of the arm subsided, and weight gain occurred. She had been previously treated with radiation therapy and stilbesterol. Some blood count and platelet depression did occur. Nonetheless, when last seen in July of 1960, or 4 years after the recurrence was observed and 2 years after Thio-TEPA, she was in good health. A 62-year-old lady died 8 months after receiving Thio-TEPA During the months she was alive, symptomatic improvement was noted, although subcutaneous nodules continued to appear on skin flaps. She did gain 6 pounds during the period of treatment. One 51-year-old patient received intravenous and intrapleural Thio-TEPA because of lung metastases. She died 8 months after beginning therapy with little if any relief of dyspnea or chest pain. Progression of the disease as shown by x-ray also occurred despite deep radiation therapy, radio-active gold, testosterone, and Thio-TEPA. The final case was a 39-year-old with widespread metastatic involvement, apparently activated by pregnancy. Pain, weight loss, and other symptoms were unrelieved by cortisone, testosterone, radiation, surgery, and Thio-TEPA.

Three cases of carcinoma of the esophagus were seen in the Tumor Clinic. Dosage was 40, 80, and 100 mg. by IM and IV routes. Patient ages were 67, 49, and 51 according to the above dosages. All had metastatic disease. None got relief from Thio-TEPA.

The results with Thio-TEPA in cases of carcinoma of the pancreas were far from encouraging. Four patients received a total of 315 mg. or an average of 79 mg. doses by IV route only. Ages were 67, 68, 73, and 76. All had widespread metastases. One elderly male got minimal subjective improvement for 20 days after Thio-TEPA (two 40 mg. courses). Two patients received no benefit from Thio-TEPA. One male patient with adenocarcinoma of the head of the pancreas, regional metastases, and secondary obstruction of the common bile duct, received 235 mg. over a 9-month period with excellent relief of pain. He was even able to go to work. Appetite and weight increased. When last examined before he was lost to follow-up, however, metastatic skin nodules were noted and a nodular liver was palpable.

Three interesting cases of malignant melanoma were studied. Dosage was 55, 120, and 130 mg. in 31, 69, and 36-year-old patients respectively. Intramuscular, intravenous, and intratumor injection methods were employed. The 36-year-old female with malignant melanoma of the right thigh had the tumor removed and Thio-TEPA therapy at time of surgery 14 months previously. She got along well until she became pregnant. Death came 5 months after the birth of her child, with inguinal, iliac and femoral node metastases. The 31-year-old patient died suddenly one month after receiving Thio-TEPA. She got relief of dyspnea and actual

decrease in size of masses on her breast and neck, although ascites from gastrointestinal tract involvement did not respond so strikingly. The final case, a 69-year-old female with malignant melanoma of the left foot and inguinal metastases felt well for several months after Thio-TEPA but died 7 months after the initial dose, with widespread metastases.

In one large series of 13 cases, carcinoma of the skin and appendages was evaluated. Dosage levels ranged from 15 to 410 mg., with an average dose of 110 mg. IV and IM doses, as well as injection into tumor masses, were employed. Ages ranged from 38 to 85, with an average age of 70.6 years. Seven patients did not improve on Thio-TEPA. In 3 cases, we were unable to evaluate results because of failure of patient to return. Of the 7 patients who did not benefit from chemotherapy, diagnoses included basal cell carcinoma of the right eyelid with metastases to the neck, squamous cell carcinoma of the maxillary sinus, 2 squamous cell carcinomas of the tongue, squamous cell carcinoma of the soft palate, squamous cell carcinoma of the face, and squamous cell carcinoma of the penis. Of the 3 cases showing some relief, one felt better for about 2 months on Thio-TEPA. He had squamous cell carcinoma of the left ear with metastases to the neck. He noted some relief of pain. Nodes in the neck seemed also to decrease in size. On the third month, pain returned and ulceration appeared over the mandible. Another patient, a 58-year-old male with basal cell carcinoma of the face, had good symptomatic relief of severe pain on 410 mg. of the drug over a 22-month interval. Prior treatment had included chemosurgery, x-ray, and surgery

of the eyelids. When last seen in the clinic, he was in good health. The final patient was a 38-year-old male with squamous cell carcinoma of the maxillary sinus and metastases to skull and jaw. He had received extensive chemosurgery prior to Thio-TEPA. During the 4 months he was on the drug, the disease did not progress, he felt well, and ate well. That was in July of 1960. In September of 1960, when last heard from, his condition was poor and he was experiencing severe pain.

Finally, 7 cases were listed under miscellaneous tumors for lack of a better classification. Dosage in this group ranged from 40 to 160 mg., with an average dose of 68.5 mg. Routes employed were intravenous and intratumor. Ages ranged from 19 to 82 years, with an average of 52 years. One patient had squamous cell carcinoma of the cervix, Grade IV, with metastases to lung and neck. She showed no response to Thio-TEPA. Another patient, a 53-year-old male, had squamous cell carcinoma of the soft tissues of the left side of the neck, with metastases to lung, primary unknown. He died 5 days after intratumor dose of Thio-TEPA. An 82-year-old female with adenocarcinoma of the endometrium, vagina and lung did not respond to 60 mg. of the drug. A 19-year-old boy with metastatic teratocarcinoma of the testes died without relief from Thio-TEPA. Another patient, a 25-year-old female with sarcoma of the right chest and widespread metastases, died without relief from all forms of therapy, including Thio-TEPA. One 40 mg. IV dose was all that was given to a 79-year-old male with liposarcoma of the arm, metastatic to the lung. He died 2 days later. Autopsy revealed only 15% of lung uninvolved by tumor. The final case, a 47-year-old female with mucinous

adenocarcinoma of the neck, primary unknown, failed to respond to the drug.

SUMMARY AND CONCLUSIONS

In conclusion, it is apparent that there is still no chemical compound which alone is capable of producing a cure for cancer in man. The advances of the past fourteen years, since the inception of nitrogen mustard in 1946, have come both from the pioneer endeavors and the carefully planned programs in a few institutions and from critically conducted empirical programs in clinical investigation. Although the number of chemical compounds useful against the many forms of cancer is small, the individual researcher should in no way be discouraged. Such investigators have fashioned new techniques and vocabulary in initiating a new era in cancer research. Their efforts have stimulated hope of similar attacks on other problems in medicine, once regarded as hopeless.

As has been pointed out previously in this paper, clinical investigations employing chemotherapeutic agents may be impeded by many variables, such as unrelated diseases occurring in the individual treated. The character and duration of the previous treatment and possible toxic effects of such treatment upon organs involved may alter a response to a chemical agent. It is impossible, also, to assign patients to a group of "untreated controls", as is customary in animal experimentation. It is understandable, therefore, that "experimental design" looks much more attractive on paper than in the actual execution of such a program when applied to man.

As with all palliative therapy, the end results of this series of patients studied at the University of Nebraska Hospital fall far short of the desired level. Nonetheless, in the individual patient in whom a satisfactory response has been obtained, even for a limited period of time, the results are most gratifying. Every doctor who has been faced with the necessity of telling a patient or his family that everything has been done, or performing a palliative operation, will realize that the use of chemotherapeutic agents in selected cases can prove to be a welcome adjunct in the handling of malignant tumors.

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