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FDA COMMITTEE CAN'T FIND "REASONABLE" EVIDENCE ALKYLATING AGENT CLINICAL USE IS CARCINOGENIC

The Food & Drug Administration has expressed concern over the prospect that alkylating agents, which are becoming increasingly valuable as anticancer drugs, present serious toxicity problems including the possibility that they may be carcinogenic themselves.

Robert Young, FDA group leader for oncology, asked the agency's Oncologic Drugs Advisory Committee to consider the evidence and offer some suggestions. The committee concluded that, as a class of drugs, alkylating agents affect fertility in humans, and in animals are carcinogenic, mutagenic and teratogenic. The committee did not agree

(Continued to page 2)

In Brief

FDA OPENS ADVISORY COMMITTEE CONSIDERATION OF NDAs, FINDS DISCUSSION IS NOT INHIBITED

ACTION ON NDAs by the FDA Oncologic Drugs Advisory Committee (*The Cancer Letter*, Sept. 3) was the first time a discussion on whether or not a new drug application should be approved has been held in public session. FDA has always insisted on closed sessions in the past, contending that public knowledge of committee actions and discussions could unduly affect a drug manufacturer's stock, before FDA makes its final decision on the NDA (the committee's decision is only advisory). FDA also has offered the same reasons for closing peer review discussions that have so far kept closed NIH study section consideration of grant applications—that open sessions would inhibit full and free criticism. Latest interpretation of the Freedom of Information Act led FDA to decide that from now on, the only justification for closing committee meetings will be if trade secrets are being discussed. Did the fact that the meeting was open inhibit the discussions? "Not with this committee," said FDA staff member Robert Young. "I think that's why they decided to start with this group. They would speak their minds regardless, and the others would know that it works okay." . . . **OCCUPATIONAL CARCINOGENS** seminar will be held at Yale Univ. Sept. 22. It is designed for industrial physicians, nurses, medical students, industrial hygienists, union officials and others interested in the field. Presentations will be made on methods for determining carcinogenicity of compounds in industry and measures to protect workers. Write to 616ABloomfield Ave., Bloomfield, Conn. 06002. . . . **RECENT ADVANCES** in Cancer Chemotherapy is the subject of a Louisiana State Univ. continuing medical education program Oct. 8-9 in New Orleans. Objective is to provide physicians with an appropriate pharmacologic and chemotherapeutic background in understanding anticancer drugs. Tuition is $50, with no fee for med students, interns or residents. Write to Rafael Sanchez, LSU School of Medicine, 1542 Tulane Ave., New Orleans, 70112.

FDA CONSIDERS STRONGER WARNINGS FOR USE OF ALKYLATING AGENTS

(Continued from page 1)

that there is sufficient evidence to prove carcinogenicity in man, although committee member Philip Schein said, "We're all very suspicious that they are carcinogenic in man."

Young discussed data developed in studies by Susan Sieber and Richard Adamson, of NCI's Laboratory of Chemical Pharmacology. They reported on the clastogenic (chromosomal damage), mutagenic, teratogenic and carcinogenic effects of various antineoplastic agents. Drugs reported on included cytoxan, chlorambucil, busulfan, TEM, HN2, Thio-TEPA and CBLL.

One of FDA's concerns, Young said, is the prophylactic use of these drugs in patients "who may already have been cured by surgery," that is, adjuvant chemotherapy. That would of course include the extremely promising use of such drugs following surgery for breast and bone cancer.

"There are two questions we want you to consider," Young told the committee. First, is there reasonable evidence that the effects are serious hazards? Second, are they class effects?"

The discussion that followed in reported here, with some editing. Quoted are committee Chairman Michael Shimkin, members Charles Moertel, Margaret Sullivan, John Whitaker, and Schein, and consultant Melvin Krant.

Shimkin: I don't think there is any question that acute leukemia incidence is greater among patients treated with alkylating agents.

Moertel: I'm not sure we have any valid evidence that anticancer agents are producing cancers in significant numbers.

Shimkin: I think the carcinogenicity of alkylating agents combined with radiotherapy is quite conclusive, in animals and man . . . About a half dozen bladder cancers have been found in patients treated with cytoxan.

Moertel: But how many thousands have been treated with cytoxan? It's likely that every patient who gets bladder cancer will be written up.

Schein: There is solid animal data on the carcinogenic effects of alkylating agents.

Shimkin: To me, there is no question that both radiotherapy and alkylating agents are carcinogenic. But that should not preclude their use. . . . The question is, should we have a statement on the package insert, you are now working with a carcinogenic agent.

Moertel: But we're talking about normal clinical use, not someone working in a nitrogen mustard plant. There is no question that alkylating agents are carcinogenic, but not necessarily in normal clinical use.

Whitaker: Cytoxan is being used to treat rheumatoid arthritis.

(A discussion developed around the point of limiting use of alkylating agents to life-threatening diseases, or more specifically as anticancer drugs).

Young: We can't sit on this until we have the final evidence. We have to decide if we need some warning.

Krant (to Schein): Suppose you get a call from a physician who has a 25-year-old woman patient who is pregnant, who obviously needs cytoxan. What do you do? Tell him to go ahead and treat her with cytoxan?

Schein: I would cite the data and advise him to tell the patient of the risks.

Krant: Would you recommend abortion (because of the mutagenic-teratogenic effects)?

Sullivan: A woman with a malignancy has enough problems without carrying a caring for a child. Radiotherapy also presents that problem.

Schein: There is no question in my mind that patients can be made permanently sterile (by alkylating agents).

Sullivan: Not always. We've had children in which the sterility was reversed.

Schein: We've had a five-year followup and have had very few in which fertility returned. . . . The question of carcinogenicity is something that should be studied in depth. We don't know.

Shimkin: Is there a consensus on the committee that as a class of drugs, alkylating agents affect fertility in humans, and in animals are carcinogenic, mutagenic and teratogenic? Should we suggest modifying their use for nonmalignant diseases?

Young: People who treat cancer understand the risks. When we start approving the use for non-fatal diseases, and for young people, we want to strengthen their (physician) thinking on what the risk can be. . . . I don't see a consensus on the committee about human carcinogenicity.

Shimkin: Who on the committee thinks alkylating agents are not carcinogenic?

Moertel: Thinks? Sure. Substantial evidence? No.

Young: We're asking for reasonable evidence.

Moertel: Okay, reasonable evidence, no.

Shimkin: It's a gray area. Is there reasonable evidence that alkylating agents produce tumors in man? (There was no response) Okay, is there no data at all?

Moertel: We can't say that.

Schein: We're all very suspicious that they are carcinogenic in man.

CANCER CONTROL DILEMMA: WHAT TO DO WITH THE SUCCESSFUL DEMONSTRATIONS

NCI's Cancer Control Program, faced this year for the first time with little money for new projects, is also coming up against the sticky question of what to do about demonstration projects which are nearing the end of their three-year contracts.

Ironically, the successful projects may be more likely to lose their NCI funding than the

unsuccessful ones.

"I don't consider the unsuccessful projects as much a problem as the successful ones." Diane Fink, director of the Div. of Cancer Control & Rehabilitation, told the division's advisory committee. "The problem is what do we do with the successful ones? Do we continue to fund them?"

"Any demonstration project must include provision for self support," said committee member Oliver Beahrs. "If they are successful, part of that success should be in lining up other funds." But Beahrs acknowledged that in some cases, promising projects which have reached the end of the three year funding period without securing ongoing non-NCI support should be supported by NCI for an additional time.

"The good programs will be hard to phase out," noted committee consultant Harold Rusch. Some could be supported by various fees, he said, but that is not possible for others. American Cancer Society support might be expected for certain programs, "but if ACS can't do it, who will? The medical schools are not apt to. Some worthwhile programs will not be continued without some NCI support."

"For an area in which the nation has been derelict for so long, to speak in terms of three to five years to establish some programs is absurd," said committee member Timothy Talbot. "Our real problem is to develop intelligent, capable, well-trained man and woman power. If we pull the plug, how can we keep people in the program that are any good? Medical schools are hard pressed. We've got to think in long range terms."

Fink had commented that the concept governing much of the Cancer Control Program was to provide seed money for demonstrations, and then "pull out and let it be picked up by other sources." When to pull out is the question.

"We're coming to a crossroads," Fink said. "A number of contracts are reaching the end of three years. We will be informing some contractors that we won't be continuing the funding, and if they are successful, then they should be picked up and funded by other means."

"How can a community replicate a successful program demonstrated elsewhere?" asked committee member Grace Monaco. Fink noted that those programs would appear in the literature, but that NCI did have a responsibility to help promote and extend the information transfer.

Committee member Louis Leone said he "supports the idea of seed money . . . but that it is possible for a project to be ended with inadequate evaluation. A good model could be lost through incomplete demonstration."

Committee member Maurice Reizen said he felt that long term contracts and grants should be kept to a minimum. "We should move the money around . . . When the staff goes out at the midpoint of a contract (for merit review) they must insist that the contractor start getting outside funding."

"But a sudden cutoff might lose a great opportunity to get additional information," said committee member William Shingleton.

Rusch said that the Cancer Control Program "will be stuck with some good projects" which will have no chance of being funded other than by NCI.

Beahrs had the last word. "It bothers me that the division may be accepting ongoing responsibility. The purpose of a demonstration project is to show how it can be done, so that others can do it. It is irresponsible for an institution to become dependent on the Cancer Control Program. They have got to learn to be independent."

SOME SUBSCRIBERS STILL HAVE NOT RECEIVED JULY 23 ISSUE; CONTACT US

Some ***Cancer Letter*** subscribers did not receive the July 23 issue, due to an oversight by the mailing department. Many of those who did not receive that issue have so notified us, but others have not.

The Cancer Letter has no way to identify which subscribers did not get that issue. Check your files; if the July 23 (Vol. 2 No. 30) issue is not there, let us know and your copy will be sent immediately.

PROSTATIC CANCER WORKSHOP REPORTS ON ETIOLOGY, DIAGNOSIS, TREATMENT

Grantees of the National Prostatic Cancer Project reported on the status of their various research programs at a recent workshop sponsored by the Project. Papers were presented on etiology & prevention, detection & diagnosis, and treatment. Selected abstracts from those presentations follow:

ETIOLOGY & PREVENTION

RNA TUMOR VIRUS-LIKE ACTIVITIES IN HUMAN PROSTATE: THEIR PRESENCE IN TISSUES AND INDUCTION IN EXPLANT CULTURES – S.K. Arya, L. Job, J. Horoszewicz, and W.A. Carter, Roswell Park

The cytoplasmic extracts of human prostatic tissues yield two classes of "particles" when centrifuged to equilibrium in a sucrose density gradient: one class bands at a density of 1.15-1.18 g/cc ("low density particles"). Both bands display endogenous DNA polymerase activity which is largely resistant to actinomycine D inhibition. The endogenous activity is stimulated by the addition of oligo (dT) and can be inhibited by omission of one of the DNA precursors. The endogenous DNA products synthesized by "high density particles" give only a marginal indication of high molecular weight RNA:DNA complexes. Most of the DNA products sediment as low molecular weight molecules. Interestingly, the tissue extracts from normal, hyperplastic and neoplastic prostate either spontaneously release—or can be induced to release—"particles" by treatment with bromodeoxyuridine. These "particles" band at a density of 1.15-1.18 g/cc in a sucrose density gradient and possess both RNA and an associated DNA polymerase activity which utilizes poly(A):oligo (dT). While these particles-associated activities need to be further characterized, our results suggest that human prostatic tissues may contain functions analogous to those of known RNA tumor viruses of other species. Because these activities are not yet fully defined and can apparently be detected in the normal prostate, it remains to be determined whether they are either typical C-type RNA viruses or, in fact, exclusively related to the process of neoplasia in the human prostate.

CYTOMEGALOVIRUS AND CANCER OF THE PROSTATE: IN VITRO TRANSFORMATION OF HUMAN CELLS WITH A HUMAN PROSTATIC CMV ISOLATE – F. Rapp, L. Geder, E. Sanford, T. Rohner, Pennsylvania State Univ.

Urogenital tissue specimens were maintained in culture for two years. Epithelioid growth was enhanced with use of collagenase digestion rather than trypsinization. Twenty of 34 prostate cancer cell cultures survived more than 10 in vitro passages, during which time 4 of 20 demonstrated epithelioid morphology. One epithelioid line (T-157) survived 32 in vitro passages. The cells demonstrated lack of contact inhibition in culture, were slightly positive in acid phosphatase tests, and reacted positively with CMV-immune sera in indirect IF tests. These cells, which were proven to be of human male origin, failed to yield infectious virus and could be re-isolated from a nodule induced by the cells when injected subcutaneously into weanling athymic nude mice. The serum of the patient from which the tumor cells were derived demonstrated high CMV antibody titers and reacted with the virus-specific membrane and intracellular antigens of CMV-transformed human cells in IF tests. A CMV strain isolated from one of the normal prostate cell cultures established an in vitro long-term persistent infection of human embryo lung cells which resulted in the development of two transformed cells lines. The transformed cells possessed CMV antigenic markers and induced non-differentiated tumors when transplanted into athymic nude mice.

The results constitute further evidence of the transforming capacity of CMV, and suggest that the virus may be oncogenic in its natural (human) host.

CHARACTERIZATION OF PROSTATIC CARCINOMA AMONG BLACKS – Cooperative Prostatic Research Group, Howard Univ. and University College Hospital, Ibadan, Nigeria.

This is a continuation of the comparative study of prostatic carcinoma in a high-risk U.S. American black and a low-risk Nigerian black population. The pathological, clinical and epidemiological aspects of the analysis will be presented.

Clinical features, plasma hormone concentrations, epidemiologic variables (such as sexual history and habits, occupational characteristics, etc.) and tumor morphology were studied in 134 American and 65 Nigerian patients with histologically confirmed prostatic carcinoma. U.S. age-matched randomly selected control patients with non-genitourinary, non-cancerous, and non-endocrinologic conditions were compared with U.S. cancer patients.

In comparing American and Nigerian black patients in the two age groups with the highest number of cases (age groups 55-64 and 65-74), there was found a marked predominance of Grade I carcinoma over Grades II and III in American blacks. However, this was not noted for Nigerian males. A comparison of the mean ages of black patients with Grade I-III carcinoma revealed that the mean ages of patients for all grades were higher in American black males than in Nigerian males. For all grades the age difference between American and Nigerian black patients was significant ($p < .05$). The difference in age-distribution of black males with carcinoma of the prostate from Ibadan, Nigeria and Washington, D.C. may be due to the difference of the age structure of the populations concerned. The preponderence of cases with lower grades in the American patients may be related to earlier diagnosis of the disease in this country.

Of the clinical cases studied, 30.7% of the American patients and 4.8% of the Nigerian patients were in Stage I when first seen; 21.1% of the American and 4.8% of the Nigerian patients were in Stage II; 10.5% of the American and 24.2% of the Nigerian patients were in Stage III; and 37.7% of the American and 66.1% of the Nigerian patients were in Stage IV. In contrast to the national trend, the majority of black patients in this country were in high stage when first seen. There was considerable difference in the two surveyed hospitals in Washington, D.C. (namely, D.C. General Hospital and Howard University Hospital). At D.C. General Hospital 38.6% of the patients were in low stage (Stages I and II) which conforms with the nationally reported statistics. In Howard University Hospital 60% of the patients were in low stage when first seen. This suggests that the stage of disease may be a function of social-economic conditions.

DETECTION & DIAGNOSIS

IMMUNOCHEMICAL STUDIES OF PROSTATIC ACID PHOSPHATASE (PAP) – N.R. Rose, B.K. Choe, E.J. Pontes, and I. McDonald, Wayne State Univ.

The objectives of these studies are to define the antigenic specificity of PAP in relation to acid phosphatase from other tissues and to provide basic information for developing immunodiagnostic methods for prostate cancer. Purification of PAP involved the use of affinity chromatography on Con A and immunoadsorbent columns. Enzyme purity was characterized by immunochemical criteria. Antigenic identity of electrophoretic or chromatographic isozyme of PAP was suggested from results obtained from neuraminidase digestion and quantitative inhibition experiments. Quantitative aspects of PAP-anti-PAP interactions were studied. Anti-PAP antibodies exhibited $K_{(rel)}$ of 2.2×10^7 to 1.2 to 10^8 liters/mole. Mole ratios of Ab/Ag were 6-8 for rabbit sera and 3.5 to 4 for monkey sera to equivalence. Radioimmunoassay (RIA) and counterimmunoelectrophoresis (CIEP) techniques were developed to detect PAP levels in biological fluids and immunofluorescent (IF) techniques were developed for PAP secreting cells. Serum and bone marrow PAP levels were determined by RIA and CIEP in 165 normal males and in 48 prostate cancer patients. The normal serum PAP level was found to be 1.6 ± 0.8 ng/100µl. The serum PAP levels of patients with malignant but non-prostate tumors fell in the normal range, whereas levels higher than 4 ng/100µl were found in patients with prostate carcinoma. Serum PAP levels determined by CIEP showed close agreement with those obtained by RIA for the same subjects. In preliminary studies anti-PAP and fluorescent anti-rabbit IgG were used to detect presumptive PAP-producing prostatic carcinoma cells metastasized to the bone marrow and/or to lymph nodes. The specificity of antibodies to PAP was tested against various acid phosphatase preparations derived from 10 different human tissues and different human cell cultures by immunodiffusion or immunoelectrophoretic techniques. Antibodies to PAP do not react with acid phosphatase (AcP) originating from other tissues. Bulk pancreatic cell AcP does not share antigenic specificity with PAP; however a subpopualtion of pancreatic cells seems to produce a small fraction of AcP which is immunologically cross-reactive with PAP. One pancreatic islet cell carcinoma produced a very high concentration of AcP cross-reactive with PAP. Further studies on antigenic structures of human AcP and on immunoassay methods for PAP are now in progress.

ENZYMES AND ISOENZYMES IN DIAGNOSIS OF PROSTATIC CANCER – J.T. Grayhack, E.F. Wendel, C. Lee, and R. Sadolowski, Northwestern Univ.

Although routine rectal examination is of value as a screening tool for early malignancy of the prostate, the frequent discovery of clinically unsuspected carcinoma in prostatic tissue removed to relieve bladder neck obstruction indicates a need for other diagnostic aids to assist in recognizing the patient with a high risk of malignancy. This need is supported by other clinical experiences. Our efforts to utilize studies of prostatic fluid to identify the patient with a significant risk of prostatic cancer are based on the presumption that a diffuse metabolic change is present in the prostate gland undergoing malignant change. Histologic studies have documented the frequent occurrence of multiple independent foci of malignancy in the prostate, supporting a concept of multicentric origin. More recently this concept has been supported by the findings of premalignant change in the benign tissue adjacent to the carcinoma and also by the finding of the reversal of lactic dehydrogenase (LDG) V/I ratio in this tissue. Since prostatic fluid is a product of epithelial cell secretion, studies of the LDH isozymes, leucine aminopeptidase, glucose 6, phosphate dehydrogenase, and acid phosphatase content of this fluid were undertaken with the hope that altered cells could be sampled and changes identified that would permit recognition of cancer of the prostate in its early stages.

To date, lactic dehydrogenase isozymes have been determined in 576 prostatic fluid specimens obtained by massage from 389 patients. The LDH V/I ratio exceeded a value of 2 in 11 of 14 patients with a histologic diagnosis of carcinoma, none of the 57 men 45 years of age or younger who had 10 or less WBC/h.p.f., and 2 of 46 patients with BPH and 10 or less WBC/h.p.f.

Although the prostatic fluid is extremely rich in leucine aminopeptidase, no consistent difference in this enzyme was noted between the patient groups with carcinoma and BPH. Preliminary data suggest a reduction in acid phosphatase concentration per milligram protein in the prostatic fluid from patients with carcinoma.

Preliminary data support the hypothesis that prostatic fluid provides a sample of the altered prostatic cell and may be used to identify metabolic changes associated with carcinoma.

TREATMENT

THE EVALUATION OF CANCER CHEMOTHERAPEUTIC AGENTS IN ANIMAL MODELS OF PROSTATIC ADENOCARCINOMA – J. Smolev, W.D.W. Heston, W.W. Scott, and D.S. Coffey, Brady Urological Institute

The availability of animal models for prostatic adenocarcinoma were reviewed, with emphasis on the biochemical, histological, and growth requirements of the Dunning R-3327-H prostatic adenocarcinoma which is transplantable in the Copenhagen/Fischer F_1 hybrid rat. Histological and morphometric analysis at both the light and electron microscopic levels indicate that this is a well-differentiated prostatic adenocarcinoma. The enzymatic profile of the tumor has been established and related to sex accessory tissue of the host. Growth rates of the tumor have been determined following hormonal manipulation. The ability of the tumor to relapse from hormone therapy has been demonstrated as well as the pattern of metastasis. This model has been evaluated and is a suitable system for screening cancer chemotherapeutic agents.

PRE-THERAPEUTIC EVALUATION FOR EXTENDED-FIELD RADIOTHERAPY OF PROSTATE CANCER – M.A. Bagshaw, Stanford Univ.

In a previous report we described the rationale for extended-field radiotherapy in prostate cancer, the requirements for pre-therapeutic evaluation of patients with apparently localized primary tumor, the results of surgical staging of lymph node involvement in the first 34 protocol patients who were studied, the radiotherapeutic technique employed, and analysis of early results and complications. At this time, the group of patients treated under the protocol has been extended to over 60. This presentation focused on an analysis of the extent of the prostatic neoplasm as has been demonstrated by lymphangiography and surgical confirmation of the lymphographic findings.

The reduction in complications which resulted from the therapeutic program described in the previous communication were demonstrated. The current status of patients who have been treated under the protocol guidelines was described, although it must be emphasized that no long-term followup is available at this time.

NEW STEROIDAL ALKYLATING AGENTS IN THE TREATMENT OF ADVANCED STAGE D CARCINOMA OF THE PROSTATE – A. Mittelman, R. Catane, G. Murphy, Roswell Park

Estramustine (Estracyt) and Prednimustine (Leo 1031 represent novel chemical combinations of estradiol and prednisolone with HN_2 and chlorambucil respectively. These compounds are being evaluated singly and in combination therapy.

Fifty patients with prostatic carcinoma (47 stage D, and 3 stage C) were given continuous oral Estracyt (Estramustine phosphate) 15 mg/kg/day. All patients had progressed on prior standard treatment. The objective and subjective response rates were 19% and 36% respectively. Six of the 50 patients are still receiving treatment for 1-3 years. One additional patient had Estracyt therapy for one year, with a complete response, which included disappearance of osteoblastic metastasis. He still continues in unmaintained remission despite the fact that Estracyt therapy was stopped because of gastrointestinal toxicity.

All patients are in good general condition and no serious side effects related to the drug have been seen. Two patients have relapsed and are again under control after the alkylating steroid, Prednimustine (Leo 1031), was added to the Estracyt regimen.

Estracyt may be given safely for a prolonged period, and has a place in the treatment of advanced prostatic cancer refractory to hormonal therapy.

Twenty-one patients with stage D prostatic adenocarcinoma who failed to respond to hormonal therapy, were treated with a combination of Estramustine (Estracyt) 600 mg/M^2/day in oral doses daily. Fifteen patients have been treated with Leo 1031 alone. Estramustine is a combination of Estradiol and nitrogen mustard and alone has shown objective responses in advanced prostatic cancer. Prednimustine is an ester of chlorambucil and prednisolone. The preliminary results (after 2-9 months of therapy) are as follows: 5 patients (24%) objective response; 9 (44%) subjective improvement. Only 5 (24%) did not benefit from the drug and 7 patients (33%) are stable. Of the 15 patients treated with Leo 1031 alone, one patient has had an unequivocal objective response and one other experienced a considerable objective improvement.

These preliminary results indicate the possible advantage of adding an alkylating agent (Prednimustine) to Estramustine in advanced prostatic carcinoma.

NATIONAL RANDOMIZED STUDY OF CHEMOTHERAPEUTIC AGENTS IN PROSTATIC CARCINOMA – D.E. Johnson, M.D. Anderson; W.W. Scott, Johns Hopkins; R.P. Gibbons, Virginia Mason Clinic; G.R. Prout, Massachusetts General Hospital; J.D. Schmidt, Univ. of Iowa; T.M. Chu, J.F. Gaeta, J. Saroff and G.P. Murphy, Roswell Park

In the 36 months since its inception, the National Prostatic Cancer Project Treatment Subgroup has randomly assigned over 360 patients with progressive advanced prostatic cancer who were no longer responsive to endocrine manipulation to either one of four different clinical studies. The initial study demonstrated a clear superiority for 5-fluorouracil and cyclophosphamide over continued conventional therapy. Beneficial responses were documented and are associated with increased survival rates and relief from pain and other symptoms. A proportionately larger number of patients obtained clinical benefit (stable and partial regression) on cyclophosphamide than on standard or 5-fluorouracil therapy. The criteria for evaluation of patients are supported by the survival data, i.e., responders have survived for a longer period of time than those patients who continued in progression.

Preliminary data from the subsequent protocols has documented a 30% response (stable and partial regression) in patients receiving oral estracyt and definite responses in patients treated with DTIC. Too few patients have been treated with Leo 1031 to offer total response rates at this time, although the early results are promising. These clinical studies have firmly established a place for chemotherapy in the management of prostatic cancer. New trials will introduce single and multiple drug chemotherapy at earlier phases of the clinical course of prostatic cancer patients.

A COMPARATIVE TRIAL OF ADRIAMYCIN (NSC 123127) AND 5-FLUOROURACIL (5-FU) (NSC 19893) IN ADVANCED PROSTATIC CANCER – A PROGRESS REPORT – W.D. DeWys, Northwestern Medical Center

Patients with advanced adenocarcinoma of the prostate who had failed on hormonal treatment were randomly assigned to receive either 5-FU (600 mg/M^2/wk) intravenously (IV) or Adriamycin (60 mg/M^2 every 3 weeks) IV. All patients had either measurable tumor or an elevated acid phosphatase level or both, which could be followed to assess response to treatment. Response was categorized as complete response if there was complete disappearance of all measurable disease or partial response if there was a greater than 50 percent reduction in the sum of the products of the horizontal and vertical tumor diameters.

Of 82 patients entering the study, 60 have been analyzed. Changes in acid phosphatase did not correlate consistently with other changes in disease status, and acid phosphatase is not currently being used as a measure of response. Of 32 patients initially treated with 5-FU, one had a partial response (PR). In 27 patients treated first with Adriamycin, two experienced a PR and one a complete response. On crossover to the opposite treatment we observed one PR in ten patients secondarily treated with f-FU and one PR in seven receiving Adriamycin as their second treatment. Most patients treated with 5-FU experienced mild or moderate toxicity and none experienced life-threatening toxicity. Toxicity with Adriamycin was more severe including two episodes of life-threatening disseminated intravascular coagulation and one lethal infection. Median survival was 26 weeks for Adriamycin and 17 weeks for 5-FU. The difference between these two drugs in response rate and in survival are not statistically significant. Both drugs are active against prostatic cancer and will be combined in future trials.

STEROIDS WITH CYTOTOXIC EFFECTS ON THE PROSTATE – F.H. Batzold, D.F. Covey and C.H. Robinson, The Johns Hopkins School of Medicine

We have undertaken a program for the development of specific irreversible inhibitors of key enzymes involved in steroid hormone biosynthesis. These inhibitors result from compounds bearing potential alkylating groupings which are unmasked at the active site by the target enzyme. Development of this type of inhibitor might provide novel and interesting cytotoxic agents.

We have already reported preliminary findings on two novel acetylenic steroid analogs which are potent, irreversible in vitro inhibitors of Δ^5-3-ketosteroid isomerase from P. testosteroni.

In the studies to be reported here we have shown that these compounds each produce dose-dependent shrinkage of the ventral and dorsal lateral prostate at doses up to 20 mg/kg b.s./day for 7 days when administered either intraperitoneally or subcutaneously to intact mature male rats. Studies with one of these compounds in castrate male rats showed that it did not block the effect of exogenous testosterone propionate, thus arguing against cyproterone-like effects. That the effect on the prostate is not due to estrongenic activity was shown by bioassay in the immature female mouse, which revealed no significant estrogenic activity.

These and other findings suggest, but do not establish, that our steroid analogs may be inhibiting the biosynthesis of androgens which stimulate prostatic growth.

The conjugated allenic ketones derived from the acetylenic steroid analogs discussed above have now been synthesized and characterized, and studies with these compounds are now in progress, both in vivo in rats and in vitro as potential inhibitors of Δ^5-3-ketosteroid isomerase and testosterone 5α-reductase.

CONTRACT AWARDS

Title: Isolation and tissue culture of human tumor cells

Contractor: Sloan-Kettering, $224,000.

Title: Resource for syrian hamsters

Contractor: Leo Goodwin Institute for Cancer Research, Ft. Lauderdale, Fla., $31,465.

RFPs AVAILABLE

Requests for proposal described here pertain to contracts planned for award by the National Cancer Institute, unless otherwise noted. Write to the Contracting Officer or Contract Specialist for copies of the RFP. Some listings will show the phone number of the Contract Specialist, who will respond to questions about the RFP. Contract Sections for the Cause & Prevention and Biology & Diagnosis Divisions are located at: NCI, Landow Bldg., NIH, Bethesda, Md. 20014; for the Treatment and Control Divisions at NCI, Blair Bldg., 8300 Colesville Rd., Silver Spring, Md. 20910. All requests for copies of RFPs should cite the RFP number. The deadline date shown for each listing is the final day for receipt of the completed proposal unless otherwise indicated.

RFP NCI-CM-67071

Title: *Synthesis of cyclophosphamide analogs and related materials*

Deadline: *Nov. 1*

The Drug Synthesis & Chemistry Branch, Div. of Cancer Treatment, desires to develop, via synthesis, potentially new antineoplastic drugs. The objective of the program is the operation of a synthesis laboratory for the design and synthesis of various phosphoramides and related compounds. Based on the current status of knowledge of the specific metabolism that cyclophosphamide must undergo in order to generate antitumor activity, we desire new series of phosphoramide mustards and related compounds for antitumor testing as well as metabolic studies.

It is anticipated that these studies will contribute significantly to the clarification of the basis for the comparative selectivity and clinical effectiveness of this widely used drug, as well as provide a number of new highly cytotoxic antitumor agents. In addition, it is hoped that the new insights into the mechanisms of selectivity gained from these studies will open the way to the design and synthesis of cyclophosphamide analogs that will be curative of some of the important forms of human cancer.

The design of new compounds should be directed towards such things as tissue specificity, selective transport and detoxification, and less mylosuppression while retaining the antitumor activity.

Specifically, the contractor shall perform the following tasks:

—Conduct research in the design and synthesis of phosphoramides and related compounds and furnish to the government samples of all compounds synthesized.

—Unless prior arrangement has been made with the project officer, the synthesis of three to five grams of each compound will be scheduled and submitted to NCI as required by the project officer. All materials prepared, including intermediates, shall be submitted to NCI for testing.

—Assay completely all materials as to identity and purity and determine physical and chemical properties as required.

—Submit data sheets giving pertinent chemical and physical properties for all compounds synthesized in a format acceptable to the project officer.

—Synthesize and furnish to NCI additional quantities of any compound.

Synthesis work on related classes of materials that show promise based on research studies may be carried out as mutually agreed upon by the contractor and the contracting officer or his designated representative.

The approximate level of effort anticipated for the performance of the initial year of this contract is two technical man years. It is estimated that the second and third contract year will require approximately the same level of effort as the initial year.

Contract Specialist: J.A. Palmieri
Cancer Treatment
301-427-7470

The Cancer Letter—*Editor* JERRY D. BOYD

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We have already reported preliminary findings on two novel acetylenic steroid analogs which are potent, irreversible in vitro inhibitors of Δ^5-3-ketosteroid isomerase from P. testosteroni.

In the studies to be reported here we have shown that these compounds each produce dose-dependent shrinkage of the ventral and dorsal lateral prostate at doses up to 20 mg/kg b.s./day for 7 days when administered either intraperitoneally or subcutaneously to intact mature male rats. Studies with one of these compounds in castrate male rats showed that it did not block the effect of exogenous testosterone propionate, thus arguing against cyproterone-like effects. That the effect on the prostate is not due to estrongenic activity was shown by bioassay in the immature female mouse, which revealed no significant estrogenic activity.

These and other findings suggest, but do not establish, that our steroid analogs may be inhibiting the biosynthesis of androgens which stimulate prostatic growth.

The conjugated allenic ketones derived from the acetylenic steroid analogs discussed above have now been synthesized and characterized, and studies with these compounds are now in progress, both in vivo in rats and in vitro as potential inhibitors of Δ^5-3-ketosteroid isomerase and testosterone 5α-reductase.

CONTRACT AWARDS

Title: Isolation and tissue culture of human tumor cells

Contractor: Sloan-Kettering, $224,000.

Title: Resource for syrian hamsters

Contractor: Leo Goodwin Institute for Cancer Research, Ft. Lauderdale, Fla., $31,465.

RFPs AVAILABLE

Requests for proposal described here pertain to contracts planned for award by the National Cancer Institute, unless otherwise noted. Write to the Contracting Officer or Contract Specialist for copies of the RFP. Some listings will show the phone number of the Contract Specialist, who will respond to questions about the RFP. Contract Sections for the Cause & Prevention and Biology & Diagnosis Divisions are located at: NCI, Landow Bldg., NIH, Bethesda, Md. 20014; for the Treatment and Control Divisions at NCI, Blair Bldg., 8300 Colesville Rd., Silver Spring, Md. 20910. All requests for copies of RFPs should cite the RFP number. The deadline date shown for each listing is the final day for receipt of the completed proposal unless otherwise indicated.

RFP NCI-CM-67071

Title: *Synthesis of cyclophosphamide analogs and related materials*

Deadline: *Nov. 1*

The Drug Synthesis & Chemistry Branch, Div. of Cancer Treatment, desires to develop, via synthesis, potentially new antineoplastic drugs. The objective of the program is the operation of a synthesis laboratory for the design and synthesis of various phosphoramides and related compounds. Based on the current status of knowledge of the specific metabolism that cyclophosphamide must undergo in order to generate antitumor activity, we desire new series of phosphoramide mustards and related compounds for antitumor testing as well as metabolic studies.

It is anticipated that these studies will contribute significantly to the clarification of the basis for the comparative selectivity and clinical effectiveness of this widely used drug, as well as provide a number of new highly cytotoxic antitumor agents. In addition, it is hoped that the new insights into the mechanisms of selectivity gained from these studies will open the way to the design and synthesis of cyclophosphamide analogs that will be curative of some of the important forms of human cancer.

The design of new compounds should be directed towards such things as tissue specificity, selective transport and detoxification, and less mylosuppression while retaining the antitumor activity.

Specifically, the contractor shall perform the following tasks:

—Conduct research in the design and synthesis of phosphoramides and related compounds and furnish to the government samples of all compounds synthesized.

—Unless prior arrangement has been made with the project officer, the synthesis of three to five grams of each compound will be scheduled and submitted to NCI as required by the project officer. All materials prepared, including intermediates, shall be submitted to NCI for testing.

—Assay completely all materials as to identity and purity and determine physical and chemical properties as required.

—Submit data sheets giving pertinent chemical and physical properties for all compounds synthesized in a format acceptable to the project officer.

—Synthesize and furnish to NCI additional quantities of any compound.

Synthesis work on related classes of materials that show promise based on research studies may be carried out as mutually agreed upon by the contractor and the contracting officer or his designated representative.

The approximate level of effort anticipated for the performance of the initial year of this contract is two technical man years. It is estimated that the second and third contract year will require approximately the same level of effort as the initial year.

Contract Specialist: J.A. Palmieri
Cancer Treatment
301-427-7470

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