Report of a Survival of Patients Receiving Immunoaugmentative Therapy

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REPORT OF A SURVEY OF PATIENTS RECEIVING IMMUNOAUGMENTATIVE THERAPY

SUMMARY

We conducted a survey of cancer patients who had received immunoaugmentative therapy (IAT) at the Burton Clinic in the Bahamas. Information on the treatments received, current clinical status, and quality of life was obtained by telephone at two time points, six months apart. Interviews were conducted with 54 patients and with next-of-kin for 25 deceased patients. Biases in the study group precluded inferential statistics. However, the following descriptive information is reported. The total of 79 subjects, all of whom were white, tended to be younger and of higher socioeconomic status than are cancer patients in general. The majority (82%) had received conventional cancer therapy prior to IAT, and 86% had completed their prescribed course of conventional treatment. Patients began IAT an average of 17 months following diagnosis. Prior to their first receipt of IAT, 76% of patients were ambulatory. Upon conclusion of their first course of IAT, 33% of patients reported becoming more ambulatory; 56% described no change in performance status; and 29% reported appetite improvement. Twenty-one patients (27%) had been tested for HIV antibody prior to our study; one had tested positive. Nineteen of these patients (24%) were also tested for hepatitis B, with four testing positive. During the six-month period of this study, three more patients were tested for both viruses and an additional patient was tested for hepatitis B only. All four tested negative. Although biases in this dataset precluded a valid assesment of IAT efficacy and safety, these data suggest the need for an unbiased, methodologically sound comparison of IAT and conventional cancer treatment. Such a study requires a prospective design, histologic verification of tumor type and stage, and matching on age, socioeconomic status, stage of disease and prognosis, and performance status. Subjects would have to be representative of all IAT and conventionally treated patients, respectively.

INTRODUCTION

The use of unproven or questionable cancer treatment is increasing among American cancer patients, despite advances in conventional therapies (1). This phenomenon merits concern because patients with treatable disease may be detered from availing themselves of proven therapies, and because some unproven methods may be ineffective, toxic, or otherwise unsafe (2).

Immunoaugmentative therapy (IAT) is one of the more popular unproven methods. Developed by Lawrence Burton, Ph.D., IAT therapy currently is administered from Dr. Burton's clinic in the Bahamas. Peer review evaluation of claims for IAT safety and efficacy had not been conducted. However, sufficient interest in IAT has been raised so that the office of Technical Assessment recently convened a task force to develop plans for a scientific study of IAT.

The theory behind IAT is that the immune response to tumors can be augmented to permit control of tumor growth without the toxic side-effects of conventional chemotherapy. According to the IAT brochure (3), treatment consists of a series of intramuscular injections of four immune serum protein fractions: 1) tumor complement; 2) tumor antibody; 3) blocking protein; and 4) deblocking protein. A blood sample drawn from the patient is tested to check the status of the immune system. Serum fractions are developed from necrotic tumors and the pooled blood of healthy donors. Results are computer analysed at the Burton Clinic to determine the daily dose and proper sequence of fractions for each patients (3).

However, analyses by the National Cancer Institute (NCI) revealed that IAT treatment materials were comprised of dilute blood proteins, with albumin present in the greatest concentration. None of the components described by Burton as essential to treatment activity were found in the analysis (4). Further, analyses by the NCI and independent laboratories isolated hepatitis B antigen from IAT treatment materials from six patients. One sample also yielded human immunodeficiency virus (HIV) antibody (4,5).

The current investigation was undertaken to assess the clinical safety of IAT, and to encourage IAT patients to have their blood tested for hepatitis B and HIV. To accomplish this, data on the incident of hepatitis B and HIV contamination among IAT patients were obtained. In addition, the intent was also to compare two comparable groups of patients who had metastatic disease at diagnosis: IAT patients, and patients under conventional treatment at the University of Pennsylvania Cancer Center. Both survival and quality of life were to be evaluated and compared.

Unintentional selection bias (detailed later) in the IAT patient group, and a subgroup of only 29 patients who met eligibility criteria (available biopsy reports and metastatic disease at diagnosis; Table 1) precluded valid inferences regarding the relative efficacy of IAT. The group of IAT-treated patients surveyed for this study cannot properly be considered a sample, because it was derived without recourse to appropriate sampling methodology. Thus, the use of inferential statistics was precluded.

Nevertheless, data from patients in this study represent valuable descriptive information. This is the only dataset on a sizable group of IAT-treated patients collected in a systematic way by scientist independent of Dr. Burton and his associates. Thus, it was felt important to document the results of all interviews conducted.

METHODS

Patients were conducted and asked to participate in two telephone interviews, six months apart, concerning their use of IAT. They were asked to sign consent enabling the investigators to obtain biopsy reports and other medical records from their conventional physicians. Consent forms were mailed to patients and, when signed by them, returned in a prestamped, preaddressed envelope. Patients were assured that confidentiality and anonymity would be maintained.

Patients were accrued to this study as follows:

First, patients who had received IAT were identified from the investigators' previous study of patients' use of unproven cancer therapies (1). Forty-five such patients were identified by this route. Biopsy confirmation of diagnosis and stage had previously been obtained, with patients' permission, for the earlier study. Patients in the earlier study had been accrued from unproven methods practitioners, clinics, and organizations across the country.

Second, names of additional IAT patients were provided by patients from earlier study and others, resulting in 45 new patients and a total of 90 potential study participants.

Initial contact with the first group of patients or their next-of-kin resulted in 17 patients and 15 next-of-kin of deceased patients who consented to participate. Two patients refused participation, and contact could not be established with nine patients or their next-of-kin. Two additional patients were included despite failure to contact next-of-kin because relevant clinical information was available from the previous study. Thus, 34 patients were included from the previous study.

All 45 of the new patients or their next-of-kin consented to participate, giving a total of 79 patients. Table 1 sumarizes subject accrual and provides information on medical records obtained.

Initial telephone interviews were conducted during June and July, 1986. The 79 subjects interviewed included 54 patients and, for patients deceased at the time of this initial contact, 25 next-of-kin. For the two patients under the age of 21, interviews were conducted with the parent. Demographic information -age, race, sex, occupation- and clinical information, type of malignancy, diagnostic technique, date of diagnosis, location and name and address of physician who made the initial diagnosis, were collected. Interviews also addressed patient's experience with conventional treatment and with IAT. Questions covered the sequence of treatments received;conventional treatments recommended, received and/or refused; and date began IAT. Patients were asked whether they were currently receiving IAT, and, if not, why they had stopped. Information on the range of serum injections prescribed and the frequency of clinic visits also was obtained. Quality of life questions covered performance status at first visit to the clinic, changes in appetite and performances status following the first visit, and any side effects of IAT experienced.

Patients were asked if they maintained contact with conventional medical providers, and if so, about the type of care they received, the types and results of any conventional tests or exams, and current medical status. Finally, patients were specifically asked if they had been tested for hepatitis B and/or HIV. Patients responding negatively to these questions were carefully encouraged by the interviewer to seek testing.

Follow-up interviews to obtain updated information on clinical status and interim test results were conducted six months later during January and February, 1987. The 25 next-of-kin who participated in the initial interview in vieu of deceased patients were excluded from follow-up contact. Four patients were conducted with their next-of-kin. The follow-up sample, therefore, included 50 patients. Information was obtained on current medical status, results of any recent tests or exams -including hepatitis B and HIV tests-, and on the status of the patient's IAT regimen.

RESULTS

Demographic and clinical characteristis of the study group are given in Table 2. The mean age of patients was 51 years. Subjects were evenly distributed by gender and all were white. More than half were professionals or held white collar jobs.

Based on SEER rates for all cancers among whites and on United States sensus data, the age distribution reflected in this sample differes from that expected; there is an excess of cancers in the 60-69 age group, and a corresponding deficit in the 70 age group.Thus, the IAT-patient group is somewhat younger than would be expected (6,7). Based on the distribution by occupation, the IAT patients are better educated and of higher socioeconomic status than are cancer patients in general.

In terms of specific diagnosis -Table 2-, more patients had gastrointestinal malignancies (23%) than any other type of cancer, and these patients plus those with breast, prostate, and hematologic malignancies accounted for 70% of the study group. These data suggest that the number of lung cancer patients may be lower than expected. However, given the relatively short expected survival for most patients with lung cancer, and a bias in this population toward longer survival -discussed later-, the small number is not surprising -none of the four lung cancer patients was alive at the time of the first interview-.Forty-four patients (56%) indicated that their disease was metastastic at diagnosis, although this was confirmed for only 29 subjects, as noted previously.

As Table 3 indicates, the majority of patients (82%) received conventional cancer therapy as their initial treatment; 10% went directly for IAT treatment following diagnosis; and 6% first received some other unproven treatment. Additional patients received conventional therapy after receiving IAT; in all, 75 patients (95%) are known to have received conventional cancer treatment. Most patients (86%) completed conventional treatment as prescribed.

Close to half of all subjects indicated that their disease had progressed prior to initial receipt of IAT. At the start of their first visit to the Burton Clinic, 76% of subjects were ambulatory; 11% were partially bedridden; and only one patient was entirely bedridden.

By the end of that visit, which included the first course of IAT, 44 patients (56%) reported no change in their clinical status, and 26 patients (33%) indicated that they had become more ambulatory (Table 3). This further underscores the unusual composition of this group, that is, the need to travel to the Bahamas for treatment biased the sample toward ambulatory patients. This created selection pressure toward those who were likely to survive for longer periods.

Patients began IAT an average of 17 months after diagnosis, and most (63%) completed IAT as prescribed (Table 4). Less than one-third of all patients slightly less than half of those who continued to be followed by a conventional physician had been tested for hepatitis B or HIV exposure by the time of the initial interview received tests for both viruses; one patient was tested for hepatitis only, and two of those tested for HIV received only that single test. Four patients tested positive for hepatitis B, one of whom also tested positive for HIV antibody. During the six month follow-up period, only four more patients elected to seek hepatitis B testing, and three of these were also tested for HIV. None of these patients tested positive for either agent.

Table 4 also describes patient's current vital status. Fifty patients (63%) are alive an average of 65 months since diagnosis. The mean survival time for 29 deceased patients was 59 months, and the mean survival for all 79 patients was 63 months. These survival data reflect the bias toward longer survival in this group, as the majority of subjects studied had an expected survival of 36 months or less, based on tumor site and stage alone.

One of the claims often made for IAT as well as for other unproven treatments is that patients are not subjected to the debilitating side-effects that accompany radiation and chemotherapy, and that they enjoy better quality of life. Quality of life indicators were examined for this group of IAT patients. Although most patients (86%) indicated that they were ambulatory prior to starting treatment, 33% reported that they became more ambulatory following their initial sequence of IAT treatments. Twenty-nine percent reported and improvement in appetite following the first visit. Only 3% of patients reported adverse side effects of IAT (data not shown).

DISCUSSION

This study group was notable for its willing cooperation. The great majority of patients and next-of-kin of deceased patients responded positively to the request for participation in this study, and were enthusiastic about providing information about IAT.

Patients, however, were not responsive to previously announced NIH warnings concerning the possible contamination of IAT, and only four patients responded to our encouragement that they obtain tests for hepatitis B and HIV (their results were negative). In general, patients neither believed nor trusted the NIH warnings, feeling that they were simply part of a broad effort to discredit IAT and the Burton Clinic. Of the 19 patients whose conventional physicians had performed tests for hepatitis prior to our contact, four were found to be positive, of the 21 patients who had been tested for HIV prior to our contact, one had been found positive.

Among all patients tested, four of 23 patients, or 17%, tested positive for hepatitis B, and one of 24 patients, or 4% tested positive for HIV antibody. This one HIV-positive patient is believed to be the same individual reported positive by the NCI. These data do not prove that the infections were acquired via the immune serum treatments. However, these rates are high enough to require more careful, controlled testing of the immune serum and its preparation.

Given the physical difficulty and expense associated with receiving treatment in the Bahamas, it is not surpising that IAT patients surveyed were younger, better educated, white, and of higher socioeconomic status than are cancer patients in general. However, such patients are known to live longer than do cancer patients who are older, of ethnic minority groups, and of lower socioeconomic status (8,9). The study group, therefore, is not representative of cancer patients in general. Moreover, these demographic differences bias the IAT patient group toward longer survival.

Most IAT patients had completed all or part of conventional therapy before their first visit to the Burton Clinic, and most were ambulatory at that point. This factor introduces another bias toward longer survival in the study group; a random sample of patients with the same medical background would likely include fewer ambulatory patients.

These characteristics make it impossible to draw valid inferences from this dataset concerning treatment efficacy and safety. It is not possible to determine the extent to which these biases contribute to the observed survival distribution. The deficiencies of this dataset underscore the need for an unbiased, methodologically sound comparison of IAT and conventional cancer treatment modalities.

Because a randomized clinical trial does not appear feasible, a prospective study design must be applied. Sample size requirements would make it impossible to use a single tumor site. Therefore, subjects should be selected from a population of patients with uniformly poor prognosis, such as patients with distant or visceral metastasis at the time of diagnosis. Median survival time for patients with metastatic disease of diagnosis is 12-18 months, with little variation by type of conventional treatment (10). All such patients treated by Dr. Burton could be compared to a representative sample of similar patients from a large teaching hospital or cancer center.

Histologic verification of the tumor type and stage would be one of the eligibility criteria. Data on all treatments received and prescribed, with appropriate dates would also be necessary, as would clinical and performance status prior to and following treatment. Finally, demographic data, including socioeconomic indicators, would be obtained.

Such a study is required in order to evaluate the relative safety and efficacy of IAT compared to conventional treatments. A major concern, as in any non-randomized study, would be that the two groups might differ on unknown unmeasured factors that were prognostically significant. Such factors clearly would not be amenable to adjustment. However, because the samples would be selected from patients with uniformly poor survival, with little treatment variation across patients, it is unlikely that unknown factors of great significance would exist.

A problem of possibly greater import, suggested by the current study population, is that the groups might differ enough by age, socioeconomic status, and performance status that they would not be truly comparable, despite use of adjustment techniques. If such a difference did exist, use of highly significant levels of type I and II error levels would ensure that only large treatment differences would be judged significant. To preclude potentital bias, sampling would have to take age, socioeconomic status, and performance status into account.

In summary, the emphasis in assembling this study sample was to accrue patients known to be alive and continuing IAT as of the last contact. That emphasis, necessary to fulfill our goal of encouraging patients to seek hepatitis and HIV testing, resulted in an unintentional bias toward patients with longer survival, obviating our second goal of comparative clinical analysis.

Patients who had not responded favorably to treatment were much less likely to be included in the sample. However, without knowing both the fraction of IAT treated patients that the study group represents and the survival experience of a representative sample of patients, it is not possible to determine the extent of the bias. The ability to derive unbiased inferences based on observations in a sample requires that the probability of being included in the sample is not affected either the outcome or the characteristics under study. Thus, a valid comparison of IAT treatment efficacy was not possible on the basis of data obtained for this study, nor is it possible to generalize data presented here to other IAT patients.

Our data suggest the need for an appropriately designed study of IAT, conducted in a manner convincing to both conventional medical practitioners and to Dr. Burton and his colleagues.

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TABLE 1; SUBJECT ACCRUAL AND MEDICAL RECORDS OBTAINED

	NUMBER
Number of names received	90
declined participation	2
could not locate	9
NUMBER OF PATIENTS STUDIED	79
Medical Records not obtained	12
Consent forms for acces to medical records not returned	5
Unable to contact to obtain consent for medical records	3
Refused consent to provide access to medical records	3
Medical records not received	1
Medical Records Obtained	67
Disease not metastatic at diagnosis	33
Extent of disease at diagnosis unknown	2
Biopsy data not definitive	1
Patient received other unproven treatments	2
Total subgroup with available medical records confirming metastatic or inoperable disease at diagnosis.	29

TABLE 2; SUBJECTS DEMOGRAPHIC AND CLINICAL CHARACTERISTICS AT DIAGNOSIS N=79

AGE	NUMBER	(%)
-<39	9	(11)
40-59	28	(35)
60-69	30	(38)
->70	11	(14)
Unknown	51	years
median	54	years
SEX		
Male	40	(51)
Female	39	(49)
RACE		
White	79	(100)
OCCUPATION		
Professional	9	(11)
Other White Collar	35	(44)
Blue collar	8	(10)
Homemaker	20	(25)
Student/Child	4	(5)
Unknown	3	(4)

TUMOR SITE	NUMBER	(%)
GASTROINTESTINAL	18	(23)
BREAST	14	(18)
PROSTATE	11	(14)
HEMATOLOGIC	12	(15)
MELANOMA	5	(6)
HEAD & NECK	5	(6)
LUNG	4	(5)
BRAIN/CENTRAL NERVOUS SYSTEM	3	(4)
GYNECOLOGIC	1	(1)
OTHER	6	(8)
STAGE OF DISEASE		
Metastatic/inoperable	44	(56)
Local	32	(41)
Unknown	3	(4)

TABLE 3; TREATMENTS AND CLINICAL CHARACTERISTICS OVER TIME N=79

TREATMENTS RECEIVED	RECEIVED FIRST		RECEIVED NEXT	
	Quant	(%)	Quant	(%)
Surgery	52	(66)	4	(5)
Chemotherapy/radiation	13	(16)	28	(35)
Burton (IAT)	8	(10)	39	(49)
Other	5	(6)	3	(4)
Unknown	1	(1)	2	(2)
Only initial treatment received	-	-	3	(4)

CONVENTIONAL TREATMENT COMPLETED AS PRESCRIBED

	Quant	(%)
YES	68	(86)
NO	7	(9)
Not known if conventional treatment prescribed	3	(4)
Conventional treatment not prescribed	1	(1)

DISEASE PROGRESSED PRIOR TO BEGINNING IAT

	Quant	(%)
YES	38	(48)
NO	13	(16)
UNKNOWN	28	(35)

PERFORMANCE STATUS	AT START OF FIRST BURTON CLINIC VISIT		AT END OF FIRST VISIT		AT 6 MONTHS	
	Quant	(%)	Quant	(%)	Quant	(%)
AMBULATORY	60	(76)	--	--	45	(83)
MORE AMBULATORY	--	--	26	(33)	--	--
PARTIALLY BEDRIDDEN	9	(11)	--	--	3	(6)
ENTIRELY BEDRIDDEN	1	(1)	--	--	1	(2)
UNKNOWN	9	(11)	9	11	1	(2)
DECEASED	--	--	--	--	29	(37)
NO CHARGE	--	--	44	(56)	--	--

TABLE 4: CLINICAL AND VITAL STATUS SUBSEQUENT TO THE START OF IAT
TIME FROM DIAGNOSIS TO START OF IAT.

MEAN	16.8	MONTHS
MEDIAN	5.0	MONTHS

IAT COMPLETED AS PRESCRIBED	Quant	(%)
YES	50	(63)
NO	26	(33)
UNKNOWN	3	(4)

TESTED FOR HEPATITIS	QUANT	(%)	NUMBER POSITIVE
YES	23	(29)	4
NO	31	(39)	
UNKNOWN	1	(1)	
DECEASED (NO TEST PRIOR TO DEATH)	24	(30)	

TESTED FOR HIV	QUANT	(%)	
YES	24	(30)	1
NO	31	(39)	
UNKNOWN	7	(9)	
DECEASED (NO TEST PRIOR TO DEATH)	17	(22	

VITAL STATUS AS FOLLOW UP		
ALIVE (MEAN TIME FROM DIAGNOSIS: 65+27.9 MONTHS)	50	(63)
DECEASED (MEAN SURVIVAL: 59 +53.3 MONTHS)	29	(37)

SURVIVAL TIME FROM DIAGNOSIS FOR 79 STUDY PATIENTS		
MEAN	69 MONTHS	(+38.7 MONTHS)
MEDIAN	60 MONTHS	

*25 AT INITIAL INTERVIEW, 4 AT FOLLOW UP.