Chapter 2. Methodology

Summary

The project involved a survey of two CAM cancer treatment sites identified by the NCCAM. Our project staff visited the two sites and asked CAM providers to identify their best cases. As the visitation team worked with the clinic staff physicians and reviewed the cases the latter had recommended, new cases suggested themselves to the clinic staff. These additional patient files were also screened by the visitation team based on the criteria for a best-case series established by the National Cancer Institute (NCI). The process of identifying the cases therefore was an interactive one. Promising cases were identified, and these patients were contacted to obtain permission for us to abstract their files. After consents were obtained, patients were interviewed by telephone; or if the patients were deceased, their next of kin were interviewed. All data collected from abstraction forms and the interview were summarized in a case report form. Cases identified as "best cases" based on NCI criteria, were further analyzed. All pertinent clinical data (radiologic scans, pathology slides) were identified, and clinical material was requested from the original institution. If the original clinical material was still available, it was sent to the Southern California Evidence-Based Practice Center (SCEPC).

A Best-Case Series

A "best-case series" differs from other forms of clinical evidence in that the cases are purposively selected because they are thought to be the best examples of improved patient outcomes as a result of treatment. In other words, cases are not selected randomly and are not representative of the "average" or "typical" case. Furthermore, there are no control cases that would facilitate a comparison of patient outcomes with and without the treatment in question — making it difficult, if not impossible, to establish a cause-and-effect relationship between treatment and outcome. A best-case series relies on assumptions about patient outcomes in the absence of treatment, and consequently requires very rigorous documentation of the patient's clinical status. This information is then used by clinical experts to make judgments about outcomes in similar patients treated with the best available conventional therapy. The difference in actual outcomes compared to this assessment of expected outcomes provides the basis for conclusions regarding the potential efficacy of the treatment in question. Best-case series are useful to help identify therapies that have sufficient promise of efficacy to justify the time and resources for more rigorous study, such as a clinical trial.

OCCAM Protocol for Best-Case Series

For this study, we used criteria developed by the Office of Cancer Complementary and Alternative Medicine, a part of the National Cancer Institute. These criteria require the following process:

1. Documentation of the diagnosis of cancer. The patient's cancer should be documented by obtaining tumor tissue and having it examined by a pathologist. The pathologist's report should be included in the case summary.

2. Evaluation of the appropriate antitumor endpoint. The only reliable antitumor endpoint that can be documented in a best-case series is demonstrable and reproducible reduction of tumor size. Tumor measurements are made before treatment, during treatment, and after treatment is complete. An objective response is considered to be at least a 50 percent decrease in the area (cross product of the diameters) of the tumor with no increase in any other lesions.

3. The patient must not be receiving any other treatment for his/her cancer. To document an antitumor effect based upon individual patient histories, the patient must have a documented, measurable tumor just before the CAM modalities are given. While the CAM modalities themselves may have multiple components, they must not be given with any other cancer treatments.

4. A record of previous anti-cancer treatments.

5. Documentation of sites of the cancer. At least one recurrent or metastatic cancer should be documented histologically. The date at which recurrence or metastatic disease was first noted should be provided.

6. Description of the patient's general medical condition. The age, sex, and any other previous or concurrent illnesses or significant medical conditions should be carefully documented.

7. Description of the treatment administered. The treatment that was felt to result in the antitumor response should be described.

A complete best-case series should contain:

1. Demographic data:
    a. Age
    b. Sex
    c. Date of primary diagnosis
    d. Date alternative treatment initiated
    e. Listing of all prior therapy and dates of therapy for the malignant disease.

2. Documentation of disease prior to therapy:
    a. Pathology report of primary
    b. Pathology reports documenting recurrent or metastatic disease
    c. Reports of all X-rays, CT scans, bone scans, and MRI or other imaging studies documenting the presence of known sites of tumor(s) prior to alternative treatment

d. Clinical summary denoting all signs and symptoms related to disease, the presence of other malignancies, and all nonmalignant conditions.

3. Documentation of treatment:
    a. Dates and doses of all treatment administered, including supportive care and all other drugs (other than the CAM therapy) that are administered concurrently.

4. Documentation of response:
    a. Date a response is observed
    b. Copies of all x-ray reports or other imaging studies on first date response is observed
    c. Tumor measurements of all known sites of disease that are not demonstrable on the imaging studies (e.g. skin lesions, lymph nodes) to document reduction in tumor size. This information should be provided for each date of patient evaluation
    d. Date of last visit and status and/or date and cause of death
    e. Pathology reports of biopsy of autopsy findings any time after initiation of unconventional treatment.

5. Documentation of highest toxicity during treatment by organ system and grade.

Both objective and subjective outcome measures (including quality of life) can be included.

Study Design

1. The project was conducted according to the following sequence (see Figure 1):

2. NCCAM identified two CAM providers who were treating cancer with a CAM therapy and secured their agreement to participate in the project.

3. The CAM providers were asked to identify their best cases, that is, those patients whom they judged benefited most from therapy.

4. The patients were contacted by the clinics to secure permission for their files to be reviewed, for the research team to contact them for an interview, and for permission to contact their other medical providers and request their patient files and records.

5. A research team from Southern California Evidence-Based Practice Center (SCEPC) visited both clinics to abstract patient files identified as potential best cases.

6. Following review of the patient abstraction records by the research staff, copies of the most promising patient files for inclusion in a best-case series were sent to SCEPC, where summaries of abstracted information were later checked against those files for accuracy.

7. The patients were interviewed to further confirm the medical information obtained from the charts, to identify any relevant medical information or procedures not previously identified, and to complete a Health-Related Quality of Life instrument.

8. Additional medical records were sought from the patients' other providers.

Development of the Instruments

Abstraction Instrument

Several instruments were created for this study. A draft abstraction record was created based on our previous experience assessing the office files of CAM practices. This instrument incorporated the criteria established by NCI for a best-case series (see above). Each clinic was asked to provide examples of their files (de-identified) for the team to test the abstraction form. The abstraction form is shown in Appendix A. This instrument was used in the clinics to record the relevant information from the patient files.

Case Report Instrument

Following the clinic visit and consent of the patients, the SCEPC team received copies of the patients' full files. A second instrument, the case report form (Appendix B), was developed to enable the team to summarize the cases and to arrange the information to establish the chronology of the disease and its treatment. The case report form also allowed identification of the significant events surrounding the treatment and any significant information that was not in the file (x-rays, biopsies etc.). Two versions of this instrument were produced. In the first, the information was described using medical terminology. This version, which also included columns to record information on when records were requested and the status of the request, was intended for the interviewer. A second version, designed for the patient, was written in lay terminology and included only the events and the dates of the events (also shown in Appendix B.) This form was sent to the patient prior to the interview. During the patient interview, the interviewer had both forms.

Interview Instrument

The interview instrument (Appendix C) was developed by the research team to collect the following information: basic demographic data, health related quality of life information, details of the patient's conventional treatment for cancer if applicable, details of the patient's use of CAM therapy, reasons for seeking alternative care, and reasons for choosing this particular CAM therapy. In addition, patients were asked to confirm the treatment events and dates summarized on the case report instrument which they were sent and asked to review prior to the interview.

Health-Related Quality of Life Instrument

The research team reviewed the literature on HRQOL instruments for cancer. Three Cancer Quality of Life surveys appear in the literature most frequently. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30) is cited often both in the United States and around the world. The Functional Assessment of Cancer Therapy – General (FACT-G scale) is cited more frequently in the U.S. literature than the QLQ-C30 and has several sub-scales that have been created for specific cancers. The Functional Living Index – Cancer is also used frequently in the United States. All three surveys have been shown to have valid psychometric properties (Schipper, 1984). We chose the QLQ-C30 because of its

widespread use and ease of administration. The instrument has 7 items on general health status, 21 items that refer to health status in the past week, and 2 general measures of overall physical condition and quality of life (see Appendix C, pages 7 – 9).

Research Staff

Five trained abstractors (three physicians, one oncology nurse, and one medical sociologist) performed the chart abstraction in the clinics. The three physicians are board-certified internists, and two are directors of programs in integrative medicine and have expertise in CAM therapies. The third physician is director of a chronic-pain clinic and manages a multidisciplinary team that includes practitioners of alternative therapies. The nurse has practiced in oncology wards, hospices, and palliative care units in several countries for over 30 years. The medical sociologist is a health services researcher at RAND who has been involved in abstraction studies in chiropractic over the past 10 years. A fourth physician, also trained in integrative medicine and practicing CAM therapies, participated in writing the case reviews and the case reports. This physician and the medical sociologist, who was responsible for training the other staff, conducted all the patient interviews.

Human Subjects

The following procedures were used to ensure patient confidentiality and informed consent:

1. The CAM provider obtained the patient's consent for us to view and abstract the files. When consent could not be obtained prior to the clinic visit, all files were de-identified.

2. The CAM provider sent a letter and three consent forms drafted by SCEPC to the patient for his or her signature:

    a. Consent to review the files and to contact the patient
    b. Consent to complete a short HRQOL interview
    c. Consent to pursue other medical files of the patient from either other providers or institutions.

    In addition, patients were asked to provide verbal consent to receive, by registered mail, a summary of their medical care and to participate in the interview.

3. The patient's signed consent forms were then sent to the provider/medical institutions at which the patient was receiving traditional cancer treatment.

Data Sensitivity

Data collected for this project were private and sensitive. Data abstracted from medical records documenting the patients' cancer and their treatment as well as data collected from telephone interviews (name, phone number, age, gender, quality of life) contained information that could be damaging to the individuals if revealed. Furthermore, patients may not have

wanted their providers of traditional care to know they were also receiving CAM treatment. If released, such information could possibly damage a patient's treatment, employment, and insurability. A data-safeguarding plan was instituted using guidelines established by RAND.

Safeguarding Procedures

A data-safeguarding plan was instituted using guidelines established by RAND. To prevent linkage of data to a patient, the front sheet was removed from the interview and abstraction forms and filed separately from these forms.

The patients' traditional care providers were asked to copy and provide the portions of the patients' medical files that contained information regarding the cancer treatment. This information could include radiographic films, scans, and laboratory reports. Histological slides, if any, were also requested (a detailed list of the information we sought was provided to each physician). The files received from providers were handled identically to the interview and medical record data.

Clinic Visits

Immuno-Augmentation Therapy (IAT)

Immuno-Augmentation Therapy (IAT) was developed by Lawrence Burton Ph.D. It is based on the theory that the immune system attacks cancer cells but also controls the rate of the attack by a blocking protein to prevent toxic damage to the liver. The theory is that cancer cells multiply when four factors of the immune system fail to recognize and destroy them (Center for Alternative Medicine Research in Cancer website, 1999; National Cancer Institute website, 1999; Office of Technology Assessment (Princeton University website), 1990). Cancer occurs not through a deficiency in the immune system but in the controlling mechanism that deals specifically with cancer. The therapy claims to treat the immune system—the competence of the immune system—not the cancer as such (IAT Clinic website, 2001). [Immunosupression occurs and the anti-tumor activity, the inhibitor system must be reactivated.]

The four factors that fail in the immune system are given in the therapy through daily injections of reconstituted blood: a deblocking protein from pooled blood serum of healthy donors, which is said to remove the tumor-blocking factor that prevents the immune system from detecting the cancer; tumor antibody 1, a combination of alpha 2 macroglobulin with other immune proteins (IgG and IgA) derived from pooled blood serum of health donors; tumor antibody 2, an antibody complement that stimulates the antibody, also derived from healthy donors but differing in potency; tumor complement, a substance derived from the blood clots of patients with many types of cancer, that activates the two tumor antibodies.

The therapy consists of two evaluations daily, five days a week, of the immune system to determine the relevant components in the blood by use of a spectrophotometer. The data reveal the relative activity of the tumor kill process and immune response (IAT Clinic website, 2001). The amount of serum is calculated for each patient. Through the use of subcutaneous self-injections, the serum is prescribed in timing and sequence. While all treatment initially is at the clinic and may be over a lengthy period, subsequent treatment may be done at home, interspersed with visits to the clinic for reassessment.

The Immuno-Augmentation Therapy (IAT) Clinic is located in Freeport, Bahamas. A team of four researchers (two physicians, a nurse, and a medical sociologist) spent four days in the clinic identifying and abstracting patient files. Because all the patients had already signed a consent form to allow their records to be reviewed as part of the clinic's normal procedure, no additional consent was necessary at this stage. Although the clinic staff was to have identified the best cases prior to the team's arrival, it proved to be more productive for the team, in discussion with the lead physician in the clinic, to identify likely cases and have staff pull charts during the visit. Because this clinic is dedicated to cancer treatment and because it has been in existence for some time, the number of files was very large. In addition, because many of the patients had been attending the clinic for more than 15 years, their files were rather large. The team reviewed a total of 300 patient card indexes, of which approximately 60 were chosen as possible cases. Each of these case files was independently reviewed by the two physicians on the team and with the clinic physician. Once a case was identified (using the NCI criteria) by the reviewers as a possible candidate, the information was abstracted.

Naltrexone

Naltrexone is an opiate antagonist used for treating heroin addiction and has been used to treat persons with HIV and AIDS. Its primary proponent is Dr. Bernard Bihari (Bihari, 1999). The theory for the use of low-dose Naltrexone for cancer is that it raises the levels of beta-endorphins and metenkephalins that are capable of slowing down cancer growth. Many tissues of the body have opioid receptors on their membranes for endorphins (White, 2000). The immune system is primarily regulated by the endorphins. Since AIDS involves an immune deficiency, Dr. Bihari and his colleagues (Bihari, Ottomanelli, Orbe, et al., 1998) explored using Naltrexone for this condition. In the process, they discovered it shrank malignancies and inhibited their growth, particularly in tissues with opiate receptors (Bihari, 2000). The direct activation of the opioid receptors, if it occurs while the cell is dividing, is thought to kill the cell (Bihari, 2000). It is also postulated that Naltrexone increases the activity of the immune system's natural killer cells and hence prevents newly forming or metastasizing cancer cells.

Taken in large doses, Naltrexone was found to have significant side effects. But taken at bedtime in doses of 3 mg, it doubles endorphin levels but leaves the body within 2 to 4 hours (Bihari, not dated). The endorphin levels and enkephalins remain elevated all the next day. The drug is self-administered by the patient.

Because the clinic selected for us to study was not dedicated solely to cancer treatment, it had far fewer cases to review than did the previous clinic. As a result, we reviewed the cases of nearly all the cancer patients. The research team comprised one physician and two other reviewers (nurse and medical sociologist). Over a three-day period, the team reviewed a total of 21 case files, all of which were abstracted. However, because the patients had not given consent to having their files reviewed prior to our visit, all files and all records within the files were de-identified prior to review, as required by the RAND Human Subjects Protection Committee. De-identification was done in the following manner. The physician was asked to identify the best cases prior to the team's visit. Patients' identifying information was then masked on the entire contents of the patient files, including all the physician's notes, laboratory reports, letters from other providers, and letters from the patients. Files were de-identified prior to abstraction and the determination of whether they represented potential best cases. The abstraction process we followed was the same as that used in the previous site.

Followup

At both clinics, we asked the clinic physician and/or staff to contact by mail those patients we wished to include in a followup interview, that is, those identified as potential best cases based on our abstraction. These patients were asked to sign three additional consent forms: 1) to have their files copied for the team; 2) to have the research team contact them for an interview; and 3) to have the research team contact their other medical providers to obtain ancillary materials such as lab reports, radiographic films, and histological slides.

Once a patient or his/her proxy (e.g., the next of kin in cases where the patient was deceased) consented to be included, we requested the clinic to forward a copy of that patient's entire file to us. The file was then reviewed a second time to develop a chronological record of the care. This record was then reviewed by two members of the team (including a physician) to ensure we had identified the important events and dates in the disease and treatment history, and to identify any additional records we might wish to seek. The patient or proxy was then contacted to establish a time for the interview and to determine if he or she was willing to review the chronology prior to the interview to confirm the events and dates. To ensure confidentiality, this chronology was sent via registered mail. It could be delivered only to the patient or, if the patient was a minor or deceased, to a proxy who had consented to be interviewed.

Interview

An interview designed to last approximately 30 minutes was conducted by members of the research team with the patient or proxy. The interview included demographic questions, a health-status and quality-of-life instrument, and a review of the treatment chronology for both traditional medical care and CAM therapy. A key component of the interview was to confirm the information included in the patient's file and to identify any additional relevant information not previously captured, such as additional surgeries, treatments, or followup studies. A HRQOL instrument was also included, and patients' reported HRQOL status is noted in the case reports. However, whereas some patients had extensive disease progression, no patients reported less than a "good" health-related quality of life, and most reported very good to excellent health-related quality of life.

Assessment of Cases

Using the information obtained from the patient interview and abstracted from the patient chart, one of the research physicians constructed a patient report for each case. The reports included a chronology of the disease course and the therapies used. Each case was reviewed and discussed by the two physicians and the medical sociologist to determine if it should be included. In determining whether a case should be recommended as a best case, we used the following inclusion criteria:

1. Histological, radiographic, or other imaging evidence for the initial presence and diagnosis of the cancer

2. Evidence of metastases, if any

3. If traditional modalities were used, evidence about what was done, the dates these treatments were provided, evidence for tumor response (or lack thereof), and evidence for whether the care was completed

4. Evidence for the start of the CAM therapy

5. Documentation of the CAM therapy

6. If possible, evidence for exclusive use of one CAM therapy

7. Evidence for tumor response following the CAM therapy.

Wherever possible, we requested the histological and imaging confirmations from the relevant institutions. Few cases met all the inclusion criteria.