Cancer Outcomes at the Hufeland (Complementary/Alternative Medicine) Klinik: A Best-Case Series Review

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**Purpose:** A best-case series review is an efficient tool with which to screen complex complementary and alternative treatments for cancer as candidates for further study. **Study Design:** The National Cancer Institute and other agencies have adopted the best-case series method to evaluate cancer treatments involving complementary and alternative medicine (CAM) for further study. The authors conducted a best-case series review of the Hufeland Klinik. Established in 1985 in Bad Mergentheim, Germany, this facility treats more than 500 cancer patients per year. Hufeland treatment includes dietary modification, injections, ozone therapy, active fever therapy, psychotherapy, and sometimes hormone therapy and/or low-dose chemotherapy. The goal of the treatment is to prolong survival and to maintain good quality of life. **Methods:** The clinic provided summaries of 27 cases in which patients with longer than expected survival had agreed to make their medical records available for review. The review involved pathologic confirmation of disease and radiologic confirmation of complete response (CR) or partial response (PR) not attributable to conventional treatment. **Results:** Based on the summaries and an exhaustive 2-year search for medical records, slides, and imaging data, 12 of 27 cases were selected for full review, and 5 (3 CRs and 2 PRs) were judged best cases. **Conclusion:** Most patients with common cancers receive conventional treatment before coming to Hufeland, and many are treated with chemotherapy and/or hormonal therapy while there. Hence, only a few could be considered for review. With 5 of 12 patients showing a treatment response, the authors conclude that the Hufeland treatment merits further study. They also recommend the development of criteria with which to evaluate best-case series reviews of complex CAM treatments for patients with advanced cancer.

**Keywords:** cancer; best-case series; complementary; alternative; holistic; complete response; partial response; survival

In the past decade, support for research on complementary and alternative medicine (CAM) for cancer has grown dramatically, and numerous clinical trials of herbal agents and specific CAM procedures have been undertaken or completed. The most successful candidates for research funds have been investigators who proposed studies of standardized single-modality interventions for which conventional research methods are well suited. Claims regarding the benefits of complex treatments customized to each patient are more difficult to evaluate. Many cancer clinics outside the United States provide such treatments, especially to patients who have failed to benefit from conventional treatment.

Few providers at CAM cancer clinics have research training or even a reliable charting system, but some are willing to allow outside investigators to study their treatments and results. Because conventional clinical research methods cannot be readily applied to the assessment of most CAM cancer clinics, the best-case series method has come into use to identify those facilities whose patients might have fared better than expected and to evaluate them as candidates for further study.

First proposed by the Office of Technology Assessment in 1990, the best-case series method was adopted by the National Cancer Institute (NCI) in 1991 for preliminary evaluation of complex CAM cancer therapies for which claims of efficacy were made. The NCI Office of Cancer Complementary and Alternative Medicine Web site publishes the guidelines "The Preparation of Best Case Series and the Conduct of Pilot Clinical Trials Using CAM Modalities." The

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guidelines allow practitioners to select for review any cases that exemplify what their treatment can do for cancer patients and specify that every best case must meet the following 4 entry criteria:

- The diagnosis of cancer must be well documented.
- There must be evidence that cancer was present at the time the unconventional treatment was started.
- The patient must have received the unconventional treatment according to the alternative practitioner's regimen.
- The patient must not have received, recently or con currently, another therapy with the potential to affect the disease.

Best cases also must fulfill at least 1 of the following outcome criteria:

- Complete response (CR): complete disappearance of all evidence of tumor for a set number of weeks.
- Partial response (PR): decrease by ≥50% in the sum of the products of the perpendicular diameters of all measured lesions in the absence of progression of any sites or the appearance of any new lesions for a set number of weeks.

Many cases proposed for a best-case series are those involving longer than expected survival based on data for age and stage from the medical literature or a population-based registry, such as the NCI's Surveillance, Epidemiology, and End Results database. However, although survival with good quality of life is the primary aim of cancer treatment, it is not interpretable as evidence of efficacy in an uncontrolled case series.5

In this report, we describe the results of our assessment of a best-case series submitted by Wolfgang Woeppe1, MD, founder and director of the Hufeland Klinik in Bad Mergentheim, Germany, to the National Foundation for Alternative Medicine (NFAM). Since 1998, NFAM has been visiting clinics that use CAM and inviting them to submit best cases. Of some 60 clinics reviewed in the first 2 years of this program, the Hufeland Klinik was found to be the most rigorous in its record keeping. Hufeland also has an international reputation that draws patients from the United States as well as other countries. For those reasons, it was selected for review.

Methods

Review Procedure
The study was approved by the Columbia Presbyterian Medical Center Institutional Review Board. Dr Woeppe1 selected the cases for review, obtained informed consent and permission to obtain medical records from the participating patients, and provided a summary of each case. The reviewers eliminated cases that, based on the summary, did not fulfill best-case criteria. For the remainder, in addition to reviewing the records on file at the Hufeland Klinik, we requested medical records including pathology slides and radiologic examinations from all the other institutions where the patient had received diagnostic assessment or cancer treatment. After document texts were translated into English, the cases were reviewed by the investigative team, including oncologists, pathologists, and radiologists at the Herbert Irving Comprehensive Cancer Center of the College of Physicians and Surgeons, Columbia University. The purpose of the pathology review was to confirm the cancer diagnosis of each case. Radiologists reviewed imaging studies in various formats to assess patients' status before and after the Hufeland Klinik treatment. The team then identified those cases that fit the best-case criteria.

The Practitioner
Wolfgang Woeppe1, MD, graduated from the medical school at the University of Wuerzburg (Bavaria, Germany) in 1971. Board certified in internal medicine (1978) and naturopathy (1984), he also studied acupuncture and neural therapy. From 1976 to 1982, he was a senior physician in the Department of Internal Medicine at Mosbach Regional Hospital (Baden, Germany). From 1982 to 1984, he worked with Josef M. Issels, MD, who developed and practiced a holistic approach to cancer therapy, at the Ringberg Klinik in Tegernsee, in the Bavarian Alps of Germany.6 Dr Issels's theories and methods have greatly influenced alternative cancer treatment programs in Europe and Mexico.7

The Hufeland Klinik
Established by Dr Woeppe1 in 1985, the Hufeland Klinik has treated more than 3000 inpatients and 500 outpatients and currently treats about 500 inpatients and 120 outpatients per year. The Klinik is located in Bad Mergentheim, a well-known health resort area famous for its mineral springs, in southwestern Germany near Heidelberg, Frankfurt, and Nuremberg.

Most patients who come to Hufeland have cancer. Hufeland treats all malignant diseases except acute leukemias, regardless of stage and prognosis. The Klinik also treats patients with some other diseases; it treats adults and children older than 5 years.

The Philosophy
According to theories first described by Alfred Pischinger,8 the body's most important systems (eg, the autonomic nervous system, hormones, blood and
lymph vessels, and connective tissue) comprise an interdependent network. Dr Woeppe1 views cancer as involving both cells and their interaction with this network, which constitutes their environment. Under conditions such as infection and psychological distress, the environment may cease to prevent cancer cells from proliferating. Under more favorable conditions, the environment may become conducive to apoptosis or redifferentiation of cancer cells. Treatment at Hufeland, therefore, does not primarily target the tumor, as conventional cancer treatment does, but focuses on the tumor's environment.

The Treatment
Upon admission, each patient is examined by a physician and has an electrocardiogram, ultrasound imaging, routine laboratory studies; and, in some cases, a chest x-ray. Depending on the results of these studies, patients may receive the basic treatment alone or with fever therapy or conventional treatment.

Basic Treatment
Basic treatment consists of the following.

Biological treatment. All patients receive daily subcutaneous or intramuscular injections of homeopathic agents, vitamins, and herbal agents and nonspecific immune stimulators (echinacea, mistletoe, fresh thymus, and microbial extracts). Proteolytic pancreatic enzymes; probiotics (symbiotic intestinal bacterial flora supplements); vitamins A, C, E; and selenium are administered orally. Twice a week, patients receive ozone therapy (autologous blood is incubated with a mixture of oxygen and ozone and/or irradiated by ultraviolet light and then reinfused) followed by an intravenous infusion. The intravenous infusion contains trace elements (magnesium, selenium, zinc), homeopathics, high-dose vitamins, and plant- or microbial-derived agents intended to eliminate toxins, alter metabolism, and stimulate the nonspecific immune system.

The basic program also includes dental work to eliminate mucosal pockets; dead, root-filled, or impacted teeth; and, if possible, amalgams. If tonsils show signs of chronic inflammation, tonsillectomy is recommended.

Patients are also offered enemas, lime-blossom and other herbal teas, and herbal and homeopathic remedies. Patients with constipation or digestive problems are encouraged to drink from Bad Mergenthaler's healing springs to activate bile flow and/or stimulate bowel movements.

Diet. All patients follow a low-fat lactovegetarian diet high in vegetables and whole grains, with some fruit. They are allowed (but not encouraged) to eat 1 serving of meat or fish per week. Frequent small meals are recommended for seriously ill patients. Patients are encouraged to avoid tobacco, caffeine, and alcohol.

Physical therapy. Nearly every day, patients receive hydrotherapy (cold water treatments and hot showers), reflexology, massages, or special treatments with electric fields.

Oxygen therapy. For at least 2 hours each day, most patients inhale oxygen; they continue to do so after discharge.

Psychotherapy. Dr Woeppe1 states, "Anyone for whom life is unconsciously a burden logically has no reason to get well, and his autonomic nervous system is programmed for death." Therefore, Hufeland offers patients a variety of approaches to help reduce the undesirable stress in their lives. Dr Woeppe1 conducts weekly group hypnosis sessions to influence the unconscious and to support the patient's will to get healthy again. A psychologist and an art therapist offer individual and group therapy sessions. Other modalities include deep relaxation exercises, respiratory biofeedback, imagery, color therapy, group singing, and walks and hikes.

Pain relief. Hufeland emphasizes the importance of complete pain relief. Conventional analgesics, as well as acupuncture, therapeutic local anesthesia, infrared (warming) therapy, subcutaneous carbon dioxide injections, and physical therapy are used for pain relief.

Fever Therapy
Patients who have no serious comorbid conditions may receive active fever therapy, in which Coley's toxins (bacterial lipopolysaccharides and other agents) are injected intravenously. Patients usually experience chills, nausea, vomiting, or headache within about 20 minutes, along with a slow rise in body temperature. The temperature should remain at 40°C or higher for several hours.

Conventional Modalities
In addition, patients without comorbid conditions may receive surgery, chemotherapy, radiation therapy, or hormonal therapy. The goal of such treatment is not so much to destroy the tumor as to suppress it enough to allow the host to keep it under control. Hence, patients who undergo chemotherapy at Hufeland usually receive lower doses or a shorter course of treatment than they would under a conven-
tional protocol. Some patients receive chemotherapy along with passive hyperthermia by pulsed electromagnetic field to about 43°C, applied either locally (e.g., to treat liver metastases, prostate cancer, or abdominal tumors) or to the whole body. Most patients with breast cancer or prostate cancer receive hormonal therapy.

Results
Initially, Dr. Woeppel submitted reports of 27 cancer cases. Based on these reports, we selected 12 cases for review. Table 1 lists the 12 cases that were reviewed. Of these, 5 met the criteria for best cases.

Pathology Review
Table 2 compares the original histologic interpretation to that of the reviewing pathologist for each of the 12 potential best cases. In 6 of the 12 cases, the reviewing pathologist confirmed the original interpretation. In colon cancer case 1, the pathology reviewer's diagnosis differed from that in the original report regarding tumor type, but the differences were not relevant to prognosis.

In ovarian cancer case 1, the reviewer's diagnosis differed from the original regarding the site of origin and was more consistent than the original with the indolent course of the disease. In mediastinum cancer case 1, the reviewer's diagnosis also differed slightly from that in the original report regarding tumor type, but the material was obtained by bronchoscopy and was too limited in quantity for a firm histologic diagnosis.

In 3 of 4 brain tumor cases, the histologic diagnosis differed. For this reason, the brain tumor cases were also reviewed separately by a pathologist at the NCI (Table 2). The NCI reviewer noted that prior treatment with chemotherapy and/or radiation therapy in cases 1 and 3 made firm histologic diagnoses difficult. The differences between the original pathologists and the reviewing pathologists did not appear to follow any specific pattern.

Radiology Review
Table 3 shows the results of the radiology review of the available films and the radiologists' conclusions regarding tumor response. Three patients were judged to have a complete response and 3 to have a partial response. However, in 1 of the latter (brain cancer case 2), the patient had received radiation therapy (without evidence of benefit at the time) shortly before coming to Hufeland and was therefore not categorized as a best case.

Table 4 lists the 15 cases that were excluded from the best-case series review. Of these, 7 (3 colon cancer cases, 1 stage III and 2 stage IV; 2 sarcoma cases; 1 lung cancer case; and 1 melanoma case) were excluded because the presence of malignant disease was not confirmed at the time treatment was initiated. Four cases (all 3 cases with advanced breast cancer and 1 with ovarian cancer) were excluded because they received conventional therapy (hormonal therapy or chemotherapy) shortly before or during treatment at Hufeland, 3 because of disease progression (an ovarian cancer case) or lack of a partial response to treatment (a stomach cancer case and a lung cancer case), and 1 (an ovarian cancer case) because slides were unavailable for pathology review. (In Germany, slides may be discarded after 10 years.)

Discussion
Since 1985, about 3000 individuals have been treated for cancer at Hufeland. Although some of these patients achieved remission and remain well, many, including all patients with metastatic breast cancer or prostate cancer, were ineligible for inclusion in the best-case series because they had received conventional and CAM treatment at Hufeland simultaneously. This exclusion limits best-case series review to patients who have cancers for which no conventional treatment is known, refuse conventional treatment, or wait a sufficient time after receiving conventional treatment for restaging to verify treatment failure. Yet many patients whose disease is spreading and not responding to treatment begin immediately to explore alternatives. Moreover, although potential best cases cannot be evaluated unless they have had repeat imaging just prior to starting the CAM treatment, complete restaging is not always performed at this time in clinical practice. The best-case series, therefore, shares many of the difficulties of any retrospective review. As Table 1 shows, even the patients whose cases we reviewed wasted little time between failing (or being failed by) conventional treatment and seeking treatment at Hufeland.

The best-case series approach to CAM treatments for cancer requires pathologic confirmation of the cancer diagnosis, evidence that cancer was present at the time the CAM treatment was initiated, no recent conventional treatment, and evidence of complete or partial response. These requirements are reasonable but not easy to fulfill. Old charts and scans are often difficult to find. Scans that are not necessary for the patient's treatment might not be covered by insurance. And few CAM practitioners, especially those who are not also conventional physicians, require patients to document their cancer diagnosis or interact routinely with the conventional physicians who treat their patients.
<table>
<thead>
<tr>
<th>Primary Site and Case Number</th>
<th>Age at Diagnosis/ Gender</th>
<th>Date of Diagnosis</th>
<th>Conventional Treatment</th>
<th>Last Conventional Treatment</th>
<th>First Visit to Hufeland</th>
<th>Status at First Visit</th>
<th>Last Contact</th>
<th>Outcome/Status at Last Contact</th>
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</thead>
<tbody>
<tr>
<td>Best cases</td>
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<tr>
<td>Urinary bladder 1</td>
<td>58/M</td>
<td>May 1989</td>
<td>None</td>
<td>NA</td>
<td>JUL1989</td>
<td>5-cm tumor in right side of bladder, right hydronephrosis, dilated right ureter</td>
<td></td>
<td>2002 Alive and well, CR</td>
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<td>Not best cases</td>
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<tr>
<td>Brain 2 (pineal)</td>
<td>15/M</td>
<td>Sep 1982</td>
<td>Radiation therapy Sep- Dec 1982, drainage procedures to Jan 1983</td>
<td>Jan 1983</td>
<td>Jan 1983</td>
<td>Scan Jan 1983 showed tumor size doubled since Sep 1982, diplopia, trunk and extremity ataxia</td>
<td>Jun 2002</td>
<td>Alive, clinical improvement, MS diagnosed 1995; improvement might have been due to RT</td>
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<tr>
<td>Brain 3</td>
<td>52/F</td>
<td>Jan 1983</td>
<td>Surgery, preoperative radiation therapy, pre-/postoperative BCNU</td>
<td>Nov 1983 (Ringberg)</td>
<td>Nov 1983</td>
<td>Tumor present on CT, paresthesias/dysesthesias left hand, abnormal reflexes, reduced general condition</td>
<td>Nov 1989</td>
<td>Clinical improvement, expired Nov 1989; no PR</td>
</tr>
<tr>
<td>Location</td>
<td>Age/F</td>
<td>Diagnosis</td>
<td>Stage</td>
<td>Treatment</td>
<td>Response</td>
<td>Follow-up Information</td>
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<td>CA125 = 94.3 (elevated), but no evidence of disease on imaging</td>
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<tr>
<td>Ovary 2</td>
<td>36/F</td>
<td>Surgery, mitomycin, then stem-cell transplant</td>
<td>Apr 1996</td>
<td>Aug 1996</td>
<td></td>
<td>2002 Alive and well CA125 = 13.8; no evidence of disease at first visit</td>
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<tr>
<td>Mediastinum</td>
<td>52/M</td>
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<td>Clinical improvement, stable through 1999, expired 2001; no PR</td>
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<tr>
<td>(pleura)</td>
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<td>Surgery, 1 cycle ifosfamide, talc pleurodesis</td>
<td>Oct 1994</td>
<td>Nov 1994</td>
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<td>Severe exertional dyspnea, slight nonproductive cough, postoperative weight loss of about 5 kg</td>
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</tbody>
</table>

PR = partial response; BCNU = 1,3 bis(2-chloroethyl)-1-nitrosourea; NA = not applicable; CR = complete response; SQ = subcutaneous; MS = multiple sclerosis; RT = radiation therapy; CT = computed tomography; MRI = magnetic resonance imaging.