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ETHICAL CONSIDERATIONS IN CANCER CHEMOTHERAPY

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Emil J Freireich

Department of Developmental Therapeutics, The University of Texas System Cancer Center, M.D. Anderson Hospital and Tumor Institute, Houston, Texas 77030

INTRODUCTION

The diagnosis of cancer still strikes fear and terror in the minds of patients and their families. It usually connotes a uniformly fatal illness and implies a progressive deterioration associated with pain, cachexia, tumor masses, and all kinds of unpleasantness. This irrational fear has been progressively lessened in recent years, directly as a result of substantial improvements in cancer treatment. It is generally appreciated in professional and lay populations that cancer is actually very treatable. Almost half of the patients who have this diagnosis will be cured by available treatment. However, the treatment of cancer brings to most minds the vision of deforming ablative surgery, or unpleasant and disfiguring radiation therapy, or unpleasant side effects of chemotherapy. This view of therapy must be modified by recent successes in cancer treatments that are curative without disfigurement, disability, or unpleasant effects. The therapy of early choriocarcinoma with methotrexate chemotherapy not only results in almost uniform eradication of the disease, but leaves a completely intact host with a normal reproductive system, as evidenced by the healthy children of mothers cured of this disease with chemotherapy. Another example might be the cure of skin cancer by chemosurgery, which results in virtually no scarring or unpleasant side effects, and another, the radiation therapy control of early cervical cancer. Thus, while cancer does have the characteristics of a progressive debilitating disease, it is no longer reasonable to react automatically with hopelessness to the diagnosis of cancer, since virtually morbidity-free treatment can offer a high probability of cure.

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Unfortunately, however, for a great majority of patients with the diagnosis of cancer there is a benefit-risk ratio to be considered and for that reason, there is an ethical problem in deciding upon the therapy.

BENEFIT-RISK RATIO

High Cure Rates

In diagnoses of cancer in the early stages with a high probability that the treatment will result in cure, say cure rates in excess of 50%, it seems relatively easy to accept significant morbidity and even a risk of mortality for such a high probability of curative treatment. However, even here choices can be difficult. As an example, is the deformation of a hemipelvectomy justified for the improved probability of cure from a sarcoma of an extremity? The recent public controversy over the choice between radical and simple mastectomy for the treatment of patients with earlier stages of breast cancer is another example. It seems clear that for certain individuals, even the improved probability of cure might not be worth the deformity and mental anguish resulting from a mastectomy or the loss of an extremity. Although there are ethical problems in circumstances where the probability of cure is quite high, such ethical dilemmas seem relatively easy to resolve in the individual instances, since one has an opportunity to balance a large benefit, that is, the curative treatment, against the expected morbidity.

Low Probabilities of Cure

The decisions become more difficult when cure rates are low and morbidity high, as in the more advanced stages of breast cancer, where with unfavorable large primaries or with detected axillary node metastases the probability of cure from radical surgery associated with radical radiation therapy might be as low as 20–30%. In these circumstances, the decision as to whether the deformity or the morbidity is acceptable is more difficult to balance against the lower probability of cure. Here the decision becomes more difficult for the therapist and the patient, and many more ethical issues can be raised.

Palliative Therapy

The estimation of the benefit-risk ratio becomes progressively more difficult in cancer diagnoses of the stages where even with the most radical and extensive treatment the probability of a permanent eradication of the disease is very low, say below 5%. In such cases, measures involving excessive toxicity or excessively deforming surgery can be taken only in circumstances where the palliation is significant. The use of quantitative and objective criteria for evaluating the benefit of palliative treatment has been

an enormous advance and a great assist to both physician and patients. For instance, complete remission, which is usually defined as complete disappearance of all signs and symptoms of malignancy associated with the return to completely normal function, adds substantially to the quality of life. Complete remissions are usually substantial in duration and are measured in years, and a substantial amount of morbidity can be tolerated for such excellent palliative results. As an example, in adult acute leukemia, median remission durations of a year are achieved in complete remission and 25% last for two years or more. In contrast, objectively documented but incomplete remissions, such as partial remissions or disease stabilization, while they do result in substantial benefit with improvement in function and in the quality of life, tend to be short in duration. Because of the persistence of disease, such remissions are frequently associated with the residual morbidity, that is, signs and symptoms resulting from the tumor. Thus, the degree of morbidity acceptable for such responses is proportionally less. As with curative treatment, the frequency of remission is quantitatively entering into the picture; thus, treatments with 85% or greater probability of complete remission are obviously treatments for which greater morbidity should be acceptable than for treatments where 5 or 10% of complete remissions are expected.

The benefit-risk considerations therefore can be summarized by stating that the potential for benefit must be known in objective, quantitative terms, and the probabilities of curative treatment, the probabilities of complete remissions, and the probabilities of other objective response must all be balanced against quantitative and qualitative statements of the expected morbidity in terms of side effects, deformation, and loss of the individual's functional capacities.

SHOULD THE PATIENT PARTICIPATE IN TREATMENT DECISIONS?

In the past, and in fact, in many countries throughout the world today, it is common practice for the physician to reserve to himself the responsibility for making the benefit-risk calculations and making recommendations to the patient based on his own personal view. It of course is implied that the physician individualizes these recommendations; that is, he considers the personality and the social situation of the patient in correctly evaluating benefit-risk ratios. However, when the range of choices increases quantitatively, and as the implications of these choices become broader, the need for the patient to participate in making the decisions becomes increasingly pressing. It will always be true that the patient will be strongly influenced by the physician's advice. But since the implications of these choices are so

significant for the future of the individual, it hardly seems reasonable or rational to exclude the patient from participation. Two circumstances where the physician might make recommendations without the patient's participation are where high curability with low morbidity is expected and, at the other extreme, where very low curability with enormous morbidity is expected. It is clear that at these extremes there may be unusual circumstances where the best course is to allow the patient simply to accept the advice of the therapist without its implications and without participating actively in the choices. However, in the overwhelming majority of situations in cancer treatment today, the range of choices is too large and the potential for benefit too great to reserve such privilege to the physician.

Two factors have resulted in a change in physicians' attitudes toward having the patient participate in the treatment decisions. The first is the improved level of knowledge about cancer and cancer treatment among the lay population in this country. Through the media, people are aware not only of the availability of choices for treatment, but also of strongly held opposing views in recommending certain treatments. It is therefore virtually impossible to find a circumstance where the patient could consent to being kept ignorant not only of the diagnosis, but of the implications of the treatment decision. The second factor, which is of growing importance, is the litigious attitude of patients toward their physicians. Should physicians make poor choices or make poor judgments about the choices that patients would have made, the potential for litigation is seriously increased. Thus, the practice of having the patient fully informed about the range of treatment options is increasingly common in our own culture and throughout the civilized world.

THE ROLE OF CONSULTATION

When extremely difficult choices are to be made that have an enormous impact on an individual's life, the attitude and knowledge of both the physician and the patient are major factors leading to the decisions that are ultimately made. The patient is at a disadvantage because of his personal involvement in the situation. Depending on his level of education, his background, and his own immediate experiences, he may be either unintelligent or even irrational, and in such circumstances, choices may be extremely poor. On the side of the physician, his own personal attitude toward the treatment has a major impact on the choice of treatment. Virtually no physician is able to present objectively the various kinds of treatment. Certainly he cannot present them unemotionally.

There are two important factors that greatly influence the physician's recommendations for treatment. The first is the extent of his knowledge and

direct experience with all of the available treatments. The second is his attitude, which is conditioned not only by his immediate experiences, but by his type of medical practice. In the first case, the balancing of benefits and risks requires extensive and up-to-date knowledge of all of the available scientific data on the best possible treatments, extensive knowledge of side effects and risks, and experience in this field. This factor of knowledge, expertise, and experience provides one of the most significant benefits of consultation to both the therapist and the patient. Virtually every patient would benefit by consultation with a physician who specializes in cancer treatment. The purpose of consultation in this setting is to expand not only the unpublished information available to influence such decisions, but also to give the patient the benefit of the cumulative experiences of the therapist chosen for a consultant. The second factor, that is, the orientation of the recommending physician, has become progressively more important. This is strongly affected by the emotional attitude of the physician. Contrast the eternal optimist who has a high expectation for favorable events of low probability, with the more pessimistic individual who is terribly concerned about the low risks of morbidity and mortality and emphasizes the negative sides of treatment. Much more important than the emotional bias of the physician is what has been called the *discipline effect.* The range of treatment choices and the quality of the advice given are affected by the primary discipline of the recommending physician. Thus, a surgeon, a radiotherapist, or a medical oncologist might present entirely different treatment options and different analyses of benefit-risk ratios. The "familiarity breeds contempt" effect results in much more favorable benefit-risk ratios for the treatments with which the therapist is familiar. Thus, in good conscience, surgeons tend to come up with better status for surgical treatment, radiotherapists for radiation therapy, and medical oncologist for chemotherapy. The discipline effect on the recommendation of cancer treatment has not been solved. It becomes even more difficult in the instance of "multi-modal" therapy where two or more modes of treatment are recommended for the patient. In this circumstance, the patient may get different benefit-risk ratios from different therapists for the same treatment recommendation. The physicians are required to work out a strategy for deciding either the sequence or the quantity of each of the modes of treatment combined in the multimodal treatment strategy. A meeting of minds among the physicians from the different disciplines provides the patient with the best opportunity to judge the choice of treatment, but it is extremely important that the broad range of treatment choices be exposed to the patients who have the knowledge, judgment, and willingness to participate in their own treatment choice. Again, consultation can serve to greatly expand the patient's options, particularly if this consultation is with physicians from other disci-

plines and ideally with experienced, qualified physicians with specialities in cancer treatment, from each of the three major treatment disciplines. While such extensive consultation might be the most expensive and therefore the least efficient mechanism it does give the patient the best opportunity to be informed in a qualitative and quantitative sense of the range of treatment decisions. Even when consultations with physicians from the same discipline are sought, the somewhat different range of treatment options are more likely than if a single physician is the recommending physician.

In summary, the more difficult the choice because of low benefit-risk ratios, the more useful consultation will be in assisting both the therapist and the patient in making a treatment choice.

THERAPY FOR THE HOPELESS PATIENT

The propensity to withhold the diagnosis and the prognosis from the patient is the greatest where the expected benefits of treatment are extremely low. There are many circumstances where the stage of the disease is such that no effective treatment, not even effective palliation exists. In such a circumstance, informing the patient that he has a inevitably fatal malignancy for which treatment offers no hope is a particularly cruel prognosis to give to a patient. There hardly seems any justification for explicitly informing patients of a completely hopeless prognosis. The consequence may be either transferral to the care of another physician, or the rapid flight to the cancer quack. Therefore, one might conclude that a choice to withhold the information about diagnosis and prognosis from the patient would be easy in these circumstances. However, this is not easy to execute, as mentioned above. With progression of the disease, the patient becomes aware that the diagnosis and prognosis are much more serious than he has been informed and then begins to suspect, in fact to resent, the withholding of such information. It seems that there should be much better treatment for hopelessness than deceit. Consultation is often helpful since the consultant may have knowledge of treatment methods not known to the original doctor. But by a large margin, the most effective treatment for hopelessness is legitimate scientific research conducted in the best qualified and the most accomplished treatment centers. Research offers real hope to the patient, particularly in circumstances where the pace of discovery of new treatments is rapid, as it is in the cancer treatment field. Major research centers are investigating treatments that almost certainly will provide real benefit to patients who would otherwise be without hope. The existence in a community such as ours of legitimate and genuinely potentially successful clinical research is an important additional motivation for informing the patient

about both diagnosis and prognosis, because participation in clinical research cannot be conducted without the participation of the patient and the physician. It is virtually impossible to have a patient participate in a research program without full and explicitly informed consent. In fact, every interpretation of our current law makes it mandatory that patients who are even considering participation in a clinical research program must be given not only complete but explicit information to allow them to consent to the research, with actual knowledge of the potential for risk as well as for benefit. Thus, the most compelling reason for including the patient in selecting treatment is the existence of clinical research programs. It should be emphasized that research provides probably the treatment of choice for patients who are without significant hope, that is, where the potential for benefit from existing treatment is extremely low. However, in all phases of cancer treatment, investigation is under way for the development of potentially better treatments. The better the quality of existing treatment, the more the difficult is the choice for participation in a clinical research treatment.

PARTICIPATION IN CLINICAL RESEARCH

It seems evident that clinical research offers every patient the potential for the best treatment for his disease. All clinical research that investigates new treatment should have as its primary objective the discovery of improved treatment. Clinical scientists who discover new treatments frequently persist in their profession; thus it is likely that a significant probability for the new treatment actually being a superior treatment must exist particularly in the hands of groups and of individuals who have a proven track record of being innovative and effective in discovering better treatment. In this circumstance, the potential for getting the best available treatment in the clinical research setting does in fact exist. There is, of course, a price to pay. Because the objective data are not sufficient to state with certainty that the new treatment is better than conventional treatment, there is always the risk that the new treatment will actually be inferior. In clinical research programs, the administration of treatments that are inferior to conventional treatment does in fact occur. But when the record is examined in retrospect, it is clear that the probability of improved treatment is much greater. The major reason for this is that treatments rarely get to the clinical research level until after they have passed through many phases of preclinical investigation. The balance of this paper therefore develops the ethical basis for participation in clinical investigation, depending on the degree of innovation being tested in the study.

Does Therapeutic Research Offer the Patient the Best Treatment?

If therapeutic research always did offer the patient the best treatment, then the decision to refer patients to clinical research centers would be relatively easy. Unfortunately, while the research is potentially the best treatment, it is not always so in fact. There are many clinical investigative situations when patients participate in research that is poorly conceived, with obscure objectives, where the treatments being investigated actually do have the potential for being worse than standard treatment. There are many published clinical investigations in which patients are asked to participate in clinical investigative procedures that had quite trivial objectives and where the patients had little or no potential for benefit. There have been published studies in which the investigators attempted to confirm the activity of dramatically increased effectiveness in prospective randomized clinical trials comparing the greatly improved treatment with the historically conventional treatment with disastrous results for the "control patients." In research institutions in the United States, the legal requirement of informed consent coupled with mandatory surveillance by a review body before clinical investigations are undertaken has served to diminish the potential risk to patients participating in clinical research. However, the advice of a physician to a patient to participate in clinical research, also carries with it the responsibility of the physician to have knowledge about the quality of the physician-scientists conducting such investigations, and further to assist the patients in determining whether participation in such projects is justified. In the best of circumstances, with highly reputable experienced clinical scientists, clinical research offers the best opportunity for the most favorable of outcomes.

Phase III: Treatments of Proven Value

Studies of the choice of initial therapy for cancer treatment almost invariably would be categorized as Phase III, meaning that the treatments being used are treatments known to be effective. Here the potential for benefit far outweighs the potential for any new risk. In this circumstance, the clinical research setting offers the patient the most favorable prospects for the best possible care. Still, important ethical problems remain. In circumstances where the expectation for cure with conventional treatment is relatively high, say more than 50%, the investigation of treatment with the potential for significantly improving these probabilities presents an important ethical problem. An example might be the use of adjuvant chemotherapy for patients with surgically controlled breast cancer. For patients who have favorable results from radical surgery, it is clear from the beneficial effects

of the adjuvant chemotherapy in poor prognosis patients that significant improvement in prognosis is potentially achievable. However, the possibility of delayed morbidity, many years beyond the possibility of any existing knowledge, exists. For instance, in the choice of adriamycin as an adjuvant to surgery for women with breast cancer, there have been no patients who have been followed 20 years after primary treatment. Thus, no knowledge about the possible morbidity or toxicity from such treatment can be evaluated. In such a circumstance, previously mentioned factors become extremely important in influencing the choice of treatment. It becomes ethically even more important in these circumstances to implement the full disclosure of information and participation of the patient in such treatment decisions.

Phase II: The Search for New Effective Treatments

The objective of the Phase II study is to discover significant benefit from treatments not known to be beneficial in a particular circumstance. Such studies are frequently conducted in patients for whom there is no known effective treatment. Thus, for patients with a low probability of receiving curative therapy, the investigation of treatment that has the potential of curing even a small fraction of patients would justify a significant amount of morbidity. However, Phase II studies can be conducted in patients who already have a very favorable prognosis. The better the prognosis in the patient, of course, the more difficult the choice. However, generally in the Phase II study, the investigator already has significant knowledge about the morbidity and the potential for harm. The most favorable circumstance is to investigate such treatments in a setting where there is existing knowledge from the diagnosis and stage of disease that the probability of benefit from conventional treatment is low, but even in this area, extremely difficult ethical choices can arise. Again, the adjuvant circumstance is an example of where individuals who have a very high probability of developing a recurrent disease, but who are currently free of any morbidity, and who receive treatment that has the potential of greatly prolonging disease-free periods, but introducing an immediate morbidity. In this situation all of the ethical problems relating to the use of the known treatment must be balanced against the potential for the unknown treatment and its side effects.

Phase I Research: New Treatment

The investigation of compounds whose effects are either totally unknown or are poorly known is usually restricted to patients who are in the hopeless situation, that is patients for whom no effective treatment remains, in terms of either palliative benefit or curative therapy. Some have suggested that the Phase I study has as its objective the description of the toxicity or the

morbidity resulting from the drug only, and that the search for benefit to the patient should not be an objective of such studies. The overwhelming majority of therapeutic scientists would reject this objective since each patient must have significant potential for benefit before he could ethically accept the potential for harm. Therefore, drugs chosen for a Phase I study must offer significant potential for benefit, and experimental plans in Phase I studies must include the possibility of reaching both effective and significant dosages and schedules of the drugs under study so that each participant of the Phase I study does have that potential for benefit. That seems to be the only significantly ethical way to conduct such studies.

Perhaps more than any other phase of clinical research the Phase I study offers a significant alternative to quackery. The therapeutic scientist should offer the patient the positive sides of the quack remedy technique; that is, the patient should have the potential for benefit emphasized in such studies so that the patient can receive the emotional support that research offers, particularly in competent clinical scientists' hands. Effective new treatments, in fact, have emerged, and while the frequency of effectiveness of such treatments is lower than the frequency of failure, it does nonetheless offer the patient a significant alternative to what the quack has to offer. It is also a significant alternative to "hospice," where relief of suffering is emphasized without substantial hope of either an improved quality or quantity of life. In the Phase I study, although potentially associated with increased morbidity and even unpleasant side effects, the aspect of hope may provide for individuals the best quality of life. The benefit of such research to the community is evident, but the benefit to the individual participating must be constantly kept in mind.

An additional benefit of clinical research is that patients and their family have the assurance that all available resources have been brought to bear on this extremely tragic and difficult problem. All concerned individuals can relieve and prevent severe guilt by conducting themselves in a way that assures that "everything possible was done."

SUMMARY

Cancer treatment has improved dramatically in the recent past. As a consequence, the range of choices has been greatly broadened. With a much larger range of choices and a larger range of treatment disciplines available, decisions regarding treatment create major ethical burdens for the physician and for the patient. The participation of the patient in such choices improves the ethical posture of the therapist, whenever that is possible, and also improves the probability that the best treatment will be administered. Clinical research plays an important role in cancer treatment, not only in

the discovery of new treatment, but in the provision of the best possible care for patients participating in such research. At all levels of clinical research, such treatment has the potential for being the best available treatment when conducted in the most professional manner. While poor clinical research, like poor conventional treatment, certainly exists, it is nonetheless true that clinical research has a permanent place in cancer treatment and provides an important alternate to cancer quackery. Virtually every patient with a malignant disease has some effective treatment available to him, even in the most hopeless circumstance, where the Phase I type of clinical investigation still offers significant opportunity and hope.