Measuring the Cost-Effectiveness of Cancer Care

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Historically, new therapeutic strategies for cancer have been evaluated on the basis of safety and clinical efficacy. However, the current national emphasis on efficiency of resource allocation has led to the inclusion of economic assessments in oncology studies. Economic assessments measure patients' health status and resource consumption associated with a therapeutic strategy, and combine these in a cost-effectiveness analysis. Study design can include prospective analysis of clinical trials, retrospective analysis of a clinical trial or administrative databases, or a decision analytic model. Economic analysis is being used increasingly in oncology and will continue to provide meaningful data to assist clinicians in determining the optimal treatment strategies for cancer patients and to help inform health policy decision-makers about the importance of specific cancer therapeutic strategies. [ONCOLOGY 9(6):523-538, 1995]

Introduction

Traditionally, the assessment of new therapeutic strategies for cancer has relied almost solely on safety and clinical efficacy. Recent concerns over escalating US health-care expenditures and with optimizing patient outcomes have led to increased interest in the economic assessment of cancer therapies as a secondary objective in the evaluation of such treatments. In particular, attention has focused on the efficiency of resource allocation in health-care delivery. New economic measures are increasingly being integrated into cancer clinical trials to assess the cost-effectiveness of therapy and patients' quality of life after treatment. These measures will improve the assessment of both the costs and benefits of cancer treatment strategies.

Given the growing recognition by clinicians, patients, and health-care financing organizations of resource constraints on the provision of health-care services, economic evaluation of new drugs and new technologies has taken on greater importance [1-3]. Economic evaluation is being used to help guide clinical practice by informing clinicians and patients about specific screening and treatment strategies. These assessments are often performed by hospital or health maintenance organization formulary committees as part of the selection process for preferred treatments within these organizations [4-6]. They are also being used increasingly by health policy decision-makers at the national level in Canada and Australia to help make funding decisions for their national health insurance systems [4,5], as well as in the United States through consensus treatment and screening recommendations [7-15].

Economic Concepts

Economic evaluation includes an assessment of both the costs and benefits of cancer therapies. The costs of care may fall into four categories:

Direct medical costs, which are the costs of medical services
Direct nonmedical costs, which are the costs incurred in receiving medical care (such as transportation to and from a bone marrow transplant center)
Indirect costs, which are the costs of morbidity and mortality due to illness
Intangible costs, which are the costs of pain and suffering related to illness.

An economic assessment of cancer treatment may include any or all of these categories of costs. Costs may be calculated from different perspectives. Costs of medical care can be computed from the viewpoint of the patient, caregiver, physician, payor, or society. The calculation of societal costs represents the total costs of the transaction, whereas the calculation of costs from the other perspectives may include only those costs relevant to that specific party. For example, a patient whose insurance requires a 20% copayment incurs a $1,000 hospitalization cost. Thus, the insurer would pay $800 and the patient would pay $200. The costs of that hospitalization episode viewed from the perspectives of the insurer, patient, and society are $800, $200, and $1,000, respectively.

An economic evaluation can measure costs from a single perspective or multiple perspectives.
Quality-Of-Life Assessments

Increasingly, investigators are interested in assessing quality of life or patients' perceptions of their health status as primary or secondary end points for cancer clinical trials [16-59]. This type of assessment is a relatively new area for cancer clinical studies. Inclusion of quality-of-life end points in clinical studies reflects the growing recognition that traditional clinical trial end points may not adequately capture the impact of cancer and cancer treatment on patients' lives. In broad terms, quality of life can be measured within clinical trials using two different measurement constructs: functional status and patient preference.

Functional Status

Functional status instruments are used to quantify the ability or limitation of patients across specific areas of functioning related to health. These areas, called "domains," generally include physical, emotional, and social functioning. Functional status instruments compare patients to standardized levels of functioning, the results of which are then quantified into a quality-of-life score. Functional status measures are further divided into global and disease-specific functional status measures. Global assessment measures, such as the Sickness Impact Profile (SIP) [60], the Medical Outcomes Study Short Form (MOS-SF-36) [61], and the Nottingham Health Profile (NHP) [62], have been widely used, and may be generalizable across populations of patients with different clinical conditions. However, global measures may not be sensitive to small changes in health status within therapeutic categories.

Disease-specific measures typically include some of the same elements measured by global assessments but are designed to be more responsive to the illness being evaluated. Various cancer-specific functional status instruments have been developed to focus on conditions experienced by cancer patients and on the adverse side effects of cancer therapies [16-59].

Patient Preference

In contrast to functional status instruments, which evaluate patient health status against standardized levels of functioning, patient preference assessments measure patients' interpretation of their health states [63-65]. Patient preference measures include developed instruments as well as specific techniques to elicit these data.

The most common instruments used to assess patient preference are the EuroQol© [66], the Quality of Well Being (QWB) scale [67], and the Mark Health Utilities Index (Mark HUI-III) [30,31,65]. Both the QWB and Mark HUI-III evaluate functional status across specific domains and then combine these measures into a single preference or utility score based on a predetermined population preference assessment for each component of the different health states described by the instrument. The EuroQol© asks patients to evaluate their current health state using a 0 to 100 scale, where 0 is the worst imaginable health state and 100 is the best imaginable state.

Preference elicitation techniques are interview methods that use risk or uncertainty explicitly to elicit patient preferences for their health states. The standard gamble[64,65] and the time tradeoff [68,69], for example, offer the patient the choice between a health state of defined impairment and an option requiring patients to take a risk on their health outcomes offering a probability of perfect health and the reciprocal probability of death. Patient preference for a given health state is calculated from the point of indifference between the two options. The economic outcome measure, quality-adjusted life-years (QALYS), is calculated using both survival and patient preference information [65].

Cost-Effectiveness Analysis

Different outcome measures can be used to assess the clinical benefits of therapy for an economic evaluation. These outcome measures are intermediate clinical end points, such as complete or partial response to treatment, and final end points, such as a change in survival. The final end points are more generalizable across all the study populations within an economic evaluation. Interpretation of economic studies in the assessment of cancer screening or treatment strategies is based on the relationship between the costs and benefits of the strategy being assessed. As depicted in Figure 1, an economic study can have four potential results: An improvement in clinical outcome at a reduced cost of medical services (+/-, upper left box) would be considered a dominant strategy and would be adopted. A strategy that resulted in an increase in the cost of medical services while yielding a reduction in clinical outcomes (-/-, bottom right box) would be considered to be dominated and would be rejected.

The other two potential results (the shaded boxes, +/- and -/+ ) are ambiguous, and their
interpretation depends on both the magnitude of the change in cost and the clinical outcome, as compared with the base-case strategy. To make a treatment decision in these ambiguous cases, cost-effectiveness analysis would be used to compare the costs of the medical services provided relative to the clinical outcome.

**Types of Economic Studies**

Economic evaluation of cancer clinical therapies can include several different types of study designs: Prospective or retrospective analysis of cancer clinical trials; Retrospective analysis of specific patient populations; Analysis of administrative databases, which describe the experience of a certain population defined by the type of health-care payer; and Decision analytic models, which predict the effectiveness of cancer therapies using existing clinical data. These designs can be used in isolation or as a component of an overall clinical and economic assessment of a new cancer screening or treatment strategy. Each of these study designs has strengths and limitations, as discussed in the following sections.

**Propective Studies**

Prospective economic studies of cancer clinical trials are based on random assignment of patient populations to treatment groups. This design protects against biases in patient assignment and ensures appropriate comparison groups for the assessment of a new therapeutic strategy. The prospective economic evaluations included in these studies are designed specifically to measure the costs and benefits of cancer therapies.

Economic evaluation can be included in all phases (I-IV) of the clinical development process. Ideally, economic models of therapy are developed in phase I, pilot testing of data collection instruments is completed in phase II, pivotal assessment of therapies is carried out in phase III, and assessments of different comparative agents or "real world" effectiveness studies of therapies are conducted in phase IV.

Economic evaluation requires examination of the clinical protocol for potential biases that might affect the economic study and review of the study population to increase the overall generalizability of the clinical trial. Assessment of economic end points may require different follow-up procedures than those needed for clinical end points, such as the addition of an economic data collection strategy. Often, the resources necessary to care for patients are recorded in the clinical case report forms, while the costs of these resources are collected outside the clinical trial.

Data sources used in resource costing efforts can include tracking patients through administrative databases, hospital billing records, physician or faculty practice plans, and outpatient laboratory billing records, as well as other billing records for home care, hospice, and infusion services. (The CHOICE study [AHCPR R01 HS08395-01/5], a project to assess the costs and outcomes of early-stage breast cancer in the elderly, includes analysis of both primary data provided by patients and physicians, as well as administrative data from patient Medicare records.) Assessment of a patient's out-of-pocket medical costs and quality of life can usually be undertaken only through direct patient assessment [3,63-65,70]. Development of an economic protocol within a cancer clinical trial requires careful coordination between clinical and economic investigators. While economic studies are increasingly common in the medical literature, many investigators and study personnel may not be familiar with all the aspects such a study. For successful implementation of the economic protocol, all study personnel should be very comfortable with the study concepts and the rationale for the design of the economic evaluation.

Unless the early budgeting process explicitly allocates funding to economic studies, implementation of these studies may be hampered by financial constraints. Resources are required for: (1) investigator support for additional data collection activities, (2) coordinator training, (3) parallel costing studies, and (4) data analysis.

Economic analysis is based on a consideration of the lifetime costs and effects of treatment or screening strategies. Yet, the observation period in most clinical trials does not extend over a patient's lifetime. Thus, prospective economic analysis may evaluate study results for two time periods: the actual duration of the study period and a projection of the impact of the therapy over a patient's lifetime. Projection models estimate unknown effects of therapy beyond the study period based on the impact of therapy during that period. Economic investigators have proposed the use of both conservative, or one-time effect, and optimistic, or continuous effect, assessments for these
Retrospective Analyses

Retrospective economic analyses have been performed on cancer clinical trials that did not originally include an economic component. These studies are limited by the lack of some patient-specific information (eg, out-of-pocket costs) and by the possibility that data in patients' medical records may be incomplete. Also, quality-of-life information for patients who receive cancer therapeutic strategies may not be retrievable retrospectively.

Even with comprehensive data arising from specific sites, such as medical records from a cancer center, economic data are frequently missing or incomplete. For example, patients may receive nonprotocol therapies, consult nonstudy physicians, and be rehospitalized outside of the cancer clinical trial center. This medical resource utilization may not be recorded on a patient's chart and therefore would not be otherwise available in a retrospective economic analysis.

Administrative Database Analyses

Administrative data bases have been widely used in the assessment of the costs of care for patients in general [72,73], and are increasingly being employed to assess the costs of care for cancer patients [74]. In recent studies, administrative data sets have been merged with the NCI tumor registry Surveillance, Epidemiology and End Results (SEER) to associate the type of health care delivery system [75] and cost of care [74] with the type of tumor classified by stage of diagnosis. Researchers matched data from the Group Health Cooperative (GHC) of Puget Sound with SEER and found differences in the total direct medical costs of care according to the combination of cancer site, period of treatment, tumor stage, and patient age [74].

Administrative data sets have also been employed to assess patterns of patient care across populations defined geographically [76-79] and demographically [80-82]. Medicare claims records have been used to evaluate the use of breast-conserving surgery and mastectomy for women between the ages of 65 and 79 with localized breast cancer [76]. Clinical trial results denoted equivalent survival between breast-conserving surgery with radiation therapy and mastectomy [83-87], and an NIH Consensus Panel recommended breast-conserving surgery with lymph node dissection and radiation therapy as a treatment option for appropriate patients [88]. However, investigators found that rates of breast-conserving surgery in Medicare patients ranged from 3.5% of cases to 21.2% of cases across different states [76]. Variation in the use of breast-conserving surgery was also documented across different geographic regions, between urban and rural settings, and by the type of hospital [76].

In these instances, treatment variation in clinical practice identifies an area that requires further study to assess whether patients are receiving optimal care. However, identification of patterns of patient care and economic analysis of these diseases and treatments based on the use of administrative data alone may be severely limited. Administrative databases usually include comprehensive data about procedures received by patients, but lack detail about the patient's clinical condition. In these data sets, the ICD-9 and CPT-4 coding systems are used to describe cancer diagnoses and treatments for billing purposes. However, these coding systems may not provide sufficient information on cancer diagnosis or comorbidities to allow for accurate identification of specific types of cancer patients, specific cancer treatments, or treatment complications.

In addition, patients may enter and exit administrative databases in a manner related to their illness. For example, if Medicaid patients' health improves, they may reenter the workforce. If these patients' salary is higher than the Medicaid upper eligibility limit, they will lose their Medicaid coverage. Alternatively, as privately insured patients become increasingly ill, they may face a cap on payments or lose their health insurance and enter the public health system. In either case, the reason for the loss of coverage would not be apparent from the administrative database.

Serious design flaws in analyses of administrative databases may also limit the generalizability of these studies. Patients are not randomly assigned to treatment groups, which may result in differences in stage of illness or comorbidities across the treatments. Thus, attempts to use these data to make comparisons between treatment groups may be inappropriate. Comprehensive longitudinal data for identifiable individuals are generally available only for the Medicare population. The services contained in an administrative database are limited to those reimbursed by the health-care program. Thus, the administrative database may include only the payments made by the health-care program, and these data may vary, depending on the patient copayment and deductibles. In the Medicaid program, the types of services that are reimbursed (such as prescriptions) differ based on the reason for patient eligibility.

Finally, results of an administrative database analysis can be generalized only to a population...
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defined by similar socioeconomic and demographic characteristics.

**Decision Analytic Models**

Decision analytic models of treatment received by patients permit the assessment of complicated clinical issues that would require years to test through prospective studies. Frequently, they combine clinical data from several different sources, such as the existing medical literature and medical chart abstraction. Decision analytic models can identify the most critical elements for an economic analysis of a treatment strategy and assess the sensitivity of the analysis to specific model parameters. (For example, one could assess the potential effects of Pap smear frequency on the diagnosis of cervical cancer for a cohort of patients)[9].

Decision analytic models have proved to be very effective in developing strategies for cancer screening [7-15] and treatment [89-93]. Often, however, the most important factors in an economic model are unknown or poorly assessed in the literature. Obviously, economic models cannot be used to address these shortcomings. Increasingly, economic models are being employed to streamline cancer clinical trials by helping investigators focus on the most critical elements to be assessed in a clinical trial.

**Economic Studies in Oncology**

Economic analysis can employ a variety of study designs with different advantages and limitations. These different types of analyses can be used in a complimentary manner for comprehensive assessment of cancer therapy. This section will review the literature on economic studies of cancer to provide examples of how investigators have reported on cost-effectiveness of cancer screening and treatment.

Several modeled or retrospective economic assessments have already been undertaken in the development of new therapeutic strategies for cancer. These include assessments of cancer screening programs [7-15] and cancer strategies [89-96]. Many of the studies did not utilize prospective economic data collection, but serve to illustrate the role of economic analysis in the design of cancer clinical treatment strategies.

**Screening Program Guidelines**

Decision analytic models have been used to develop guidelines for screening programs for breast cancer [7-9,12,15], cervical cancer [9,11,13-15], and colorectal cancer [10]. These models use the natural history of disease, the risk levels of specific groups for developing cancer, and the sensitivity, specificity, and cost of the screening program to recommend different screening frequency strategies.

In one such study, Eddy [9] compared the cost-effectiveness of different frequencies of cervical cancer screening for an average-risk, asymptomatic, 20-year-old woman. (Table 1). This analysis showed that the probability of developing invasive cervical cancer and the probability of death from cervical cancer decline only slightly as the screening frequency increases from every 4 years to every year, and yet the net costs increase dramatically. This model was used to help establish that annual screening strategies should be safe, and that the costs of a screening program could be reduced with almost no loss of effectiveness if the screening frequency were reduced after three negative results [9]. For the analysis of the cost-effectiveness of screening strategies, the decision analytic model was the ideal choice, since the time and cost of following large populations of women required for this assessment would have made a randomized prospective analysis prohibitive.

**Bone Marrow Transplantation**

Some of the newer cancer therapies, such as bone marrow transplantation (BMT), are very resource intensive, and have been the subject of several economic analyses. Despite higher initial costs, improved survival with allogeneic BMT compared to conventional chemotherapy in patients with nonlymphocytic leukemia resulted in lower costs per year of life saved for the allogeneic BMT treatment strategy [94]. The use of growth factors with autologous BMT produced clinical benefits in patients with lymphoid cancer and Hodgkin's disease [95,97], and retrospective economic evaluation of a clinical trial using medical records and hospital bills showed reduced treatment costs for growth factor treated patients with Hodgkin's disease [96].

**Autologous BMT in Metastatic Breast Cancer**—Autologous BMT has been shown to be an effective treatment for some cancer patients [94-97], but clinical trials of this treatment strategy have only recently been initiated in patients with metastatic breast cancer [98]. To provide information for physicians, patients, and other decision-makers in the absence of trial results, Hillner, Smith, and Desch developed a decision analytic model of autologous BMT for breast cancer patients based on a review of the literature and administrative billing records [90]. The model was based on a
Markov process, in which the health state or condition at a particular time point (t) is dependent on the prior health state in time (t-1). Probabilities for the occurrence of given health states and responsiveness to treatment based on clinical history were used to model a cohort of women to compare standard chemotherapy and high-dose chemotherapy plus autologous BMT. As illustrated in Figure 2, a woman enters standard chemotherapy at time t0 and can experience the following changes in her health state during the ensuing period: progressive disease, partial remission, complete remission, stable disease, or death. The probabilities of each of these alternative outcomes over a 3-month period were based on reported results in the medical literature. If a patient experienced an outcome other than death, the model recalculated her possible outcomes for the next period. The assessment of the high-dose chemotherapy strategy had a similar but more complicated series of options for each health state (Figure 3). The authors developed these models to project expected treatment outcomes to 5 years.

Costs, including hospital charges, physician services, pharmacy services, laboratory services, and outpatient chemotherapy were assigned to each health state. The total costs were then compared to survival for the two strategies (Table 2). The average costs for a woman undergoing high-dose chemotherapy/BMT and standard chemotherapy were $89,000 and $36,100, respectively. The authors report their model found the BMT treatment strategy improved survival by 6 months, at a cost of $115,800 per year of life gained.

The results of decision analytic models such as this one can be used to rationalize complex decision-making and to develop strategies to improve clinical trials.

Recent Initiatives

Several new mechanisms have been established to promote the integration of economic evaluation into cancer clinical trials. In April 1994, the National Cancer Institute hosted the NCI Economics Conference—a 2-day workshop for cancer centers and cooperative groups to discuss the integration of economic evaluation into cancer clinical trials [99]. The Cancer and Leukemia Group B (CALGB) recently formed the CALGB Clinical Economics Working Group to facilitate the integration of economic evaluation into its clinical trials [100]. The Eastern Cooperative Oncology Group (ECOG) has established an outcomes assessment committee with a similar charge. These efforts have resulted in the recent funding of an economic evaluation within an NCI protocol [101], and in the consideration of several other prospective economic assessments of new cancer therapies. Economic assessment is also being implemented in several clinical development programs for cancer treatments [99, 102].

Conclusion

Economic evaluation is playing an increasingly important role in the assessment of clinical treatment strategies for cancer patients. Physicians and patients can use the comprehensive data on the cost and effectiveness of cancer therapies emerging from economic studies to help make treatment decisions. Economic data are also being used by hospitals to inform formulary committee decision-making processes, by managed care organizations to help develop cancer screening and treatment strategies, and by pharmaceutical manufacturers to provide formulary committees and other decision-makers with data on the costs and benefits of therapies [3,6]. The data from economic analyses will afford clinical investigators an increasingly important tool to help determine the optimal treatment strategies for cancer patients and to help inform health policy decision-makers about the importance of specific cancer therapeutic strategies.

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