Will We Be Able To Care For Cancer Patients In The Future?

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The number of cancer patients and cancer survivors continues to increase rapidly amid predictions of a shortfall in physicians to care for them. In addition, newer cancer therapies have become increasingly complex and resource-intensive, compounding the impending workforce shortage. Simultaneously, the growing understanding of the biologic heterogeneity of cancer and the development of pharmacogenomics have opened up the possibility of personalized approaches to cancer diagnosis and treatment. Such personalization has been promulgated as a means of decreasing the cost of drug development, improving the efficacy of treatments, and reducing treatment toxicity. Although there have been notable successes, the fulfillment of these promises has been inconsistent. Providing care for future cancer patients will require the development of innovative delivery models. Moreover, new approaches to clinical research design, to the assessment of therapeutic value, and to the approval of and reimbursement for diagnostics and treatments are needed.

The future of cancer care is uncertain. Never before have we had so many drugs with which to treat a burgeoning population of cancer patients. Our improved understanding of the biologic heterogeneity of cancer, and the promise—sometimes specious—of pharmacogenomics to enable a personalized approach to diagnosis and treatment, are accompanied by public expectation of these improvements, but also a low tolerance for their soaring costs. With the aging of the population and the success of improved screening and diagnostics, the number of cancer patients is growing; with improved treatments, the population of survivors continues to grow as well. The number of providers to care for both, however, remains relatively stable. What then, is the future of this increasingly personalized, effective, labor-intensive, and costly cancer care for the growing population of cancer patients and survivors?

Increasing Demand for Care

An aging population, improved screening, and more effective therapies have resulted in a steadily increasing number of patients and cancer survivors. The incidence of newly diagnosed cases of cancer, although decreased slightly over the last decade, is now more than 1.5 million new cases per year.[1,2] During this same time period, more precipitously declining mortality rates, resulting from early detection and improved therapies, have left the number of patients dying of cancer at fewer than 600,000 per year. With time, these trends will significantly increase the overall number of cancer patients and survivors actively undergoing treatment or surveillance.

In addition to the increased number of cancer patients, newer cancer therapies have increased the complexity and needs of these patients, resulting in greater utilization of physician, nurse, and other health care resources per patient per unit of time. An academic cancer center in New England tracked these data and determined that in the past 9 years (2001 to 2009), the average number of physician visits per patient per year rose 28% during the first year of treatment (Figure 1; Lawrence N. Shulman, MD, personal communication, June 2010). Moreover, the number of infusion visits per patient during the first year of therapy increased by 147%. In addition to a greater intensity of resource utilization per patient, improved cure rates, prolonged survival, and increased availability of additional therapies for patients not cured, all result in a significant increase in the number of patients requiring short- and long-term care, even without consideration of the number of newly diagnosed patients. The increase in the number of patients with cancer at the same New England academic cancer center is shown in Figure 2A. Although the number of new patients seen each year increased modestly during the period 2001 to 2009, the number of patients receiving ongoing care rose 127%.
These data are even more striking for a disease such as breast cancer, for which long-term survival rates are greater than 80% (Figure 2B). The number of new breast cancer patients increased by 22% over the 9-year period, while the number of patients receiving ongoing care increased by more than 175%. Although such increases may be less pronounced for other diseases, for which survival rates are lower, the same general tenets apply. Additional improvements in treatments and outcomes will only accelerate these trends.

The hope that cancer would be able to be managed with oral agents, thereby diminishing the demand for infusion room visits, remains unfulfilled. Although the number of oral cancer therapies continues to increase, there has been an even more dramatic increase in the number of parenteral medications that require infusion room visits and close monitoring. In the past decade, the number of approved new parenteral agents was more than double that of oral anticancer agents.[3]

**Physician Shortage**

Studies have predicted that, within the next few years, the number of oncologists will be insufficient to meet the needs of patients with cancer and of cancer survivors.[4,5] The aggregate of the factors detailed above will exacerbate further the discrepancy between the number of patients requiring care and the number of medical oncologists available to provide that care.

It has been proposed that ongoing follow-up care for cancer survivors should be transitioned to their primary care physicians and/or other providers soon after completion of their treatment, thereby freeing oncologists to concentrate their efforts on caring for patients undergoing active therapy. There are two major obstacles to this approach. First, survivorship is a distinct phase for cancer patients during which they face significant physical and emotional challenges both in the short-term and long-term—and for which coordination of care between specialists and primary care providers is essential, but often missing.[6,7] Multiple Institute of Medicine committees and workshops have identified important gaps in the care of these patients. Perhaps even more daunting for the proposal to transition survivorship care to primary care providers are the data, shown in Figure 3, that demonstrate the decreasing number of trainees entering internal medicine without subspecialty training.[8] Coincident with this, recently passed health care legislation will allow millions of previously uninsured patients to avail themselves of health care coverage. Precisely at a time when the demand for, and demands on, internists are increasing, the number of primary care physicians is declining, thereby increasing further the demands on those who remain.[9,10,11] In addition to caring for the increased demands of an aging population, primary care physicians also must contend...
with the rising number and complexity of pay-for-performance and health maintenance initiatives, and stay abreast of an ever-evolving medical literature. Like the medical oncologist, the future primary care physician may face the Hobson’s choice of caring for patients with acute medical illnesses or cancer survivors who may be relatively well but at risk for cancer or treatment-related medical problems that require ongoing surveillance. It is likely, and not inappropriate, that patients requiring acute intervention will be given priority.

**Cancer Survivorship Care**

There is no coordinated strategy that is likely to increase the supply of oncologists or primary care physicians to adequately provide for the looming needs and number of cancer patients and cancer survivors in the coming decade. New, innovative models of care will need to be explored, and several cancer centers are beginning to develop new models of care utilizing “physician extenders,” such as nurse practitioners, physician assistants, and registered nurses. The use of such models may help solve at least the workforce deficiency in oncology. A collaborative practice model, in which physicians partner with such extenders, allows physicians to care for new patients and for patients with complex problems, while the extenders follow patients in treatment and provide survivorship care. In some centers, physician extenders practice independently and are able to bill for their services.

Similar models are being explored in survivorship clinics to address the gaps associated with transition of the cancer survivor’s care from active treatment to follow-up. In this model, the physician extender meets with the patient at the completion of treatment to provide a formal end-of-treatment summary and follow-up care plan for the patient. Follow-up care plans are based on data-driven guidelines developed by oncologists, appropriate subspecialists, and primary care physicians, and are linked to quality-of-care measures similar to those used for other chronic diseases.[12,13,14] Such a plan facilitates the transition from the oncologist to the primary care provider. In addition to summarizing the patient’s treatment, the document serves as a tool for both the patient and the primary care provider to identify relevant issues and provide guidance regarding the appropriate follow-up care specific to the patient’s particular cancer, treatment, and associated medical risks. Further efforts to educate primary care physicians and primary care physician extenders about cancer survivorship issues and to develop cohorts of primary care physicians and extenders interested in survivorship care also would help to address the knowledge and coordination gaps that accompany the transition of care from active treatment to ongoing follow-up.

**Improving Cancer Treatments and the Promise of Personalized Medicine**

The past decade has witnessed an explosion of knowledge and research into the biologic heterogeneity of cancer that has contributed to a deeper understanding of the differences in clinical presentation, prognosis, response to and tolerance of therapy, and risk for recurrence among persons with the same apparent cancer type. Cancer is no longer defined simply by its organ of origin; instead, it is now subdivided by biologic variables that blur old boundaries and identify numerous new subtypes that may differ dramatically in their presentation, behavior and response to therapy. With this increased understanding has come the development of newer, targeted agents that are designed to take advantage of these biologic differences. Indeed, the era of developing nonspecific, non-targeted chemotherapeutic agents to use against a broad spectrum of tumor types has largely ended; it has been replaced by one characterized by therapies directed against a particular molecular target or pathway with the promise of increased efficacy and decreased toxicity.
However, the fulfillment of this promise has been inconsistent. Although there have been successes, most notably the use of trastuzumab (Herceptin) in patients with HER2-positive breast cancer, more often the benefits of these agents have been modest, frequently associated with nontrivial toxicity, and accompanied by very high costs.

The use of bevacizumab (Avastin) in breast cancer is illustrative. In 2008, the FDA approved bevacizumab in combination with paclitaxel for the first-line treatment of metastatic breast cancer based on prolongation of progression-free survival (PFS) compared with paclitaxel alone (median PFS, 11.8 vs 5.9 months; hazard ratio [HR], 0.6; \( P < .001 \)).[15] Though not included in the original application for FDA approval, results from the AVADO trial, another randomized clinical trial that compared docetaxel (Taxotere) and bevacizumab to docetaxel alone, were also available. This latter study demonstrated a statistically significant improvement in PFS of less than one month with the addition of bevacizumab (PFS, 8.8 vs 8 months; HR, 0.61; \( P = .0001 \)). Neither trial demonstrated survival benefit. A third trial, the RIBBON-1 study, also demonstrated improved PFS, in this case varying from 2.4 to 3.6 months, depending on the agent used in conjunction with bevacizumab; however, it too showed no survival benefit associated with the use of bevacizumab. At the American Society of Clinical Oncology (ASCO) 2010 conference, a meta-analysis of these studies was presented that demonstrated improved response rates and PFS, but no evidence of a survival benefit from the addition of bevacizumab to chemotherapy for patients with metastatic breast cancer. In the meantime, bevacizumab, the cost of which is ~$90,000 per year, has been approved and used for the treatment of metastatic breast cancer. With approximately 45,000 women diagnosed annually with metastatic breast cancer, the potential cost of this therapy to the health care system is significant.

A similar example is the approval of bevacizumab for the treatment of locally advanced or metastatic non–small-cell lung cancer (NSCLC) based on an overall survival (OS) benefit of 2 months.[16] This story can be repeated with multiple agents. The EGFR inhibitor cetuximab (Erbitux) received accelerated approval in 2004 for the treatment of advanced colorectal cancer based on an improvement in response rate from 10.8% to 22.9% for the combination of cetuximab and irinotecan (Camptosar) compared with cetuximab alone in patients who had received prior irinotecan therapy. Median duration of response was increased by 1.6 months, and the time to disease progression was increased from 1.5 months to 4.1 months.[17] In 2007, the FDA granted cetuximab regular approval based on a National Cancer Institute of Canada study of best supportive care vs cetuximab monotherapy in patients with heavily pretreated metastatic colorectal cancer. The study demonstrated a survival advantage of 1.5 months in favor of cetuximab therapy.[18] The cost of 2 months of cetuximab therapy (the median progression-free survival in the study) for metastatic colorectal cancer is ~$37,000. A crude, and conservative, estimate utilizing an average patient with a body surface area of 1.5 m\(^2\), treated according to the regimen with the dose intensity reported in the published trial, yields a cost per year of life saved by cetuximab of nearly $300,000. The propensity of new agents to command high price tags is becoming well-established. More than 90% of the anticancer agents approved by the FDA over the last several years cost more than $20,000 for a 12-week treatment course.[19] In addition to allowing treatment to be tailored to a particular patient’s tumor characteristics or selecting the right drug at the right dose to improve the patient’s outcome, one of the promises of personalized medicine is that the improved understanding of the cancer genome will enhance the efficiency of the drug development process. This might be accomplished by using pharmacogenomic information to enrich a study population with potential responders, thereby permitting more limited enrollment and potentially shorter clinical trials.

This potential was fulfilled in the case of the development of trastuzumab in breast cancer, in which only patients with HER2-positive breast cancer were enrolled in a randomized trial to evaluate treatment with this anti-HER2 therapy. This allowed the study to be conducted with a quarter of the number of patients that would normally have been required—and also enabled the study to be completed in one-fifth the time.[20] Trastuzumab was subsequently brought to market in a fraction of the time and for a fraction of the cost that otherwise would have been required. Unfortunately, the synchronized development of a drug and of a corresponding pharmacogenomic test has not been the norm. In the case of cetuximab, it was four and a half years from initial approval until the results of a retrospective study demonstrated that patients with mutated K-ras tumors failed to benefit from cetuximab administration. Once it was understood that this biomarker could identify patients unlikely to benefit from the therapy, the cost-effectiveness of the drug improved dramatically.
Another example in which the development and validation of pharmacogenomics testing have added complexity and cost to the drug development process was that of the epidermal growth factor receptor (EGFR) inhibitor gefitinib (Iressa). In 2003, after gefitinib had demonstrated a response rate of 10% in early clinical trials, the drug was deemed to show sufficient clinical activity to receive accelerated approval for the treatment of NSCLC.[21] Subsequent randomized clinical trials demonstrated no survival benefit, and approval was ultimately withdrawn.[22,23] Eventually, EGFR mutations that better predicted benefit from the EGFR inhibitors were identified.[24] To date, the FDA has not revisited approval of the drug.

So, although pharmacogenomics hold the potential to improve the success, efficacy, and development costs of drugs, such benefits are not certain. Even if the use of pharmacogenomics is successful at reducing the cost of drug development, there is no guarantee that this savings will be passed on to consumers. Pharmaceutical companies endeavor to develop therapies that will extend and improve life, but they are also private enterprises that are charged with creating value for their shareholders.

**Impediments to Assessing and Creating Value in Cancer Treatments**

The means of assessing the benefits of cancer treatments, and the connection between this assessment and approval by regulatory authorities and adoption by the oncology community are not well defined. In practice, the assessment of a treatment frequently relies on a demonstration of improvement in OS, regardless of how small—although clinical surrogates, often with a tenuous connection to survival, are also used. Unfortunately, these measures may not be sufficient to truly assess the value of cancer treatments.
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