REPORT

Managing the Economic Impact of Advanced Pancreatic Cancer

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ABSTRACT

Pancreatic cancer is typically diagnosed in the late stage of the disease, making it the fourth leading cause of cancer-related death in the United States. It is also one of the few cancers with an increasing incidence, particularly in the younger population. By 2030, it is expected to become the second leading cause of cancer-related death. Patients with pancreatic cancer encounter monthly medical costs 15 times higher than those without, with costs highest in the later stages of the disease. Treatments for pancreatic cancer include surgery (available to fewer than 20% of newly diagnosed patients) and, for advanced disease, chemotherapy with gemcitabine with nab-paclitaxel or FOLFIRINOX, which can increase overall survival (OS) by a few months. Economic and outcome analyses of clinical data find no significant difference in OS between the 2 regimens, although FOLFIRINOX carries a much higher rate of serious adverse effects, limiting its use to patients with good performance status. In 2017, the FDA approved immunotherapy for patients with microsatellite instability–high or mismatch repair-deficient solid tumors, which occurs in approximately 1% of pancreatic cancer diagnoses. Several immunotherapies and targeted therapies are currently in clinical trials and may significantly alter the trajectory of the disease. However, they typically cost more than $100,000 per year, putting significant strain on payers. Thus, it is important that payers plan now for the potential arsenal of new treatments and identify opportunities to manage their utilization as well as patients with the disease to contain costs.

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For author information and disclosures, see end of text.

Pancreatic cancer is the tenth leading cancer in the United States but the fourth leading cause of cancer-related mortality. With an estimated 44,330 deaths in 2018, the ranking will likely change to the third leading cause of deaths due to cancer, slightly above breast cancer.[1] Diagnosis is typically made late in the disease, when the cancer is advanced or has spread to distant parts of the body. Thus, fewer than 20% of patients are eligible for curative surgical treatment.[2] Instead, the primary treatment is chemotherapy with or without radiation and, on the horizon, targeted therapy or immunotherapy. Given its late diagnosis, individuals with advanced pancreatic cancer have a very poor prognosis, with a relative 5-year survival rate of 8.5% overall. Even patients diagnosed with local disease (10%) have a 5-year survival rate of just 34.3%.[3]

Pancreatic cancer is one of the few cancers whose incidence is increasing. Between 2004 and 2013, the incidence rate increased about 1% in whites, although it remained stable in blacks.[2] The increase is particularly evident in younger people. An analysis of the National Inpatient Sample database found a 75% increase in the rate of pancreatic cancer discharges between 1997 and 2012 in those aged 18 to 44 years, with an overall increase of 55% in women and 31% in men.[4] By 2030, pancreatic cancer is expected to become the second leading cause of cancer-related death in the United States.[5]

Economic Costs

The most recent analysis of direct medical costs related to the total care of pancreatic cancer is based on 5262 patients with pancreatic cancer in a managed care population matched to 15,786 controls between 2001 and 2010. Mean total all-cause healthcare costs per-member, per-month (PMPM), including office visits, inpatient visits, emergency department (ED) visits, and inpatient stays, were $15,480 versus $1001 for the control group (all P <.001), with inpatient stays the highest cost driver ($9917 PMPM). In addition, costs were significantly higher during treatment for metastatic and advanced cancer compared with the initial treatment phase of nonmetastatic disease ($21,637 vs $10,358; P <.001).[6]

Inpatient costs, which drive overall costs for treatment, are rising. An analysis of data from 1997 to 2012 in the National Inpatient

Sample database found total costs nearly tripled during that time, from $24,000 per hospitalization to $68,000, even as the mean length of stay dropped by 19% (from 9.6 to 7.8 days; P <.001) along with a decrease in inpatient mortality by 6%. The number of hospital discharges also increased (28,862 in 1997 to 36,625 in 2012; P <.001). Surgical treatment was the main driver of cost for locoregional disease, whereas chemotherapy and radiation therapy were the main costs for metastatic disease. Inflation could also account for some of the cost increases. The authors hypothesize that improved care and availability of resources or earlier involvement of palliative care and a quicker transition to hospice in patients with widespread disease could help lower cost.[4] However, there is no evidence that patients are transitioning more quickly to palliative care or hospice.

Cost-Effectiveness of Current Therapies

In addition to clinical considerations, oncologists are increasingly faced with considering the cost and cost-effectiveness of available treatments to payers and patients. Thus, understanding the economic impact of current and novel therapies in relation to their clinical efficacy and impact on the patient's health-related quality of life (QOL) is important.

Gemcitabine (GEM) was approved in 1996 for the treatment of late-stage (III and IV) pancreatic cancer, based on data showing improved survival and clinical benefit as compared with fluorouracil, and it has remained the mainstay of treatment.[7] The majority of patients receive first-line treatment with nab-paclitaxel plus GEM,[8] which demonstrated a 1.8-month median increase in overall survival (OS) compared with GEM monotherapy in patients with metastatic pancreatic cancer[9]; or FOLFIRINOX, a cocktail of oxaliplatin, irinotecan, 5FU, and leucovorin, which demonstrated a 4.3-month median increase in OS for patients with metastatic pancreatic cancer compared with GEM monotherapy.[10] Patients with *BRCA*1/2 mutated tumors may benefit from treatment with GEM/cisplatin, and a small number of patients with epidermal growth factor receptor (EGFR) positive tumors may benefit from GEM/erlotinib.[11,12]

The choice of primary systemic chemotherapy is based, in part, on the patient's performance and clinical status given that there have been no head-to-head trials between the 2 regimens. In addition, the major trials for each were conducted in different populations, further limiting any comparisons.[9,10]

Three small retrospective reviews of real-world patient populations reported differing outcomes. One review of 85 patients with metastatic pancreatic cancer found an increased OS in patients treated with FOLFIRINOX compared with those receiving nab-paclitaxel + GEM, with similar toxicity (FOLFIRINOX 14 months vs 7 months; P <.02). In the nab-paclitaxel + GEM cohort, 48% of patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score 1 or higher compared with 4% of those treated with FOLFIRINOX (P = .01), suggesting, the authors noted, the importance of "appropriately selecting patients with poor ECOG PS who can benefit from GEM plus nab-paclitaxel for an adequate control of disease."[13] A second review of 75 patients, most of whom had ECOG 1 when starting first-line treatment with either FOLFIRINOX or nab-paclitaxel + GEM, found similar progression-free survival (PFS), OS, adverse effects, and treatment-related discontinuation rates between the 2 groups.[14]

A third analysis of 38 patients with unresectable locally advanced or metastatic pancreatic cancer who received FOLFIRINOX or nab-paclitaxel + GEM as first-line chemotherapy found a significantly higher response rate (RR) and PFS in the nab-paclitaxel + GEM group compared with the FOLFIRINOX cohort (40.9% vs 6.3%, P = .025; 6.5 months vs 3.7 months, P = .031, respectively), with lower rates of drug toxicity in the nab-paclitaxel + GEM group.[15]

Several economic analyses comparing the 2 have recently been published. In one, a Bucher indirect comparison method was used to estimate the comparative efficacy of each regimen. With no significant difference in OS, total treatment costs were 3.6 times higher with FOLFIRINOX ($116,087 vs $49,007), primarily due to higher rates of adverse effects. The FOLFIRINOX regimen, however, demonstrated a significantly higher PFS compared with nab-paclitaxel + GEM (hazard ratio [HR], 40.68; 95% CI, 40.51-0.91). The nab-paclitaxel + GEM combination also demonstrated superior incremental cost-effectiveness ratio (ICER) and incremental cost-utility ratio (ICUR), leading the authors to conclude greater economic value for nab-paclitaxel + GEM.[16]

However, a Markov model based on published clinical trials simulated the total costs and health outcomes of the 2 regimens, including direct medical costs of treatment, management of treatment-related costs, and provision of supportive care. It also found no significant difference in OS between the 2 regimens. The **Table**[17] shows the ICER and ICUR of the 2 regimens compared with each other and with GEM monotherapy.[17] Another economic analysis comparing the costs of FOLFIRINOX to nab-paclitaxel + GEM in a large insured US population found similar healthcare costs ($17,394 and $17,737) for first-line treatment in patients with metastatic pancreatic cancer, but higher supportive care costs, including antiemetics, hydration, and granulocyte colony-stimulating factor, for FOLFIRINOX.[18]

TABLE. Cost-Effectiveness of Nab-paclitaxel in Each Pertinent Spot and FOLFIRINOX vs GEM Monotherapy[17]

Treatment Regimen	Comparator	ICER	ICUR
Nab-paclitaxel + GEM	GEM	$144,096/LY	$204,369/QALY
FOLFIRINOX	GEM	$253,163/LY	$372,813/QALY
FOLFIRINOX	Nab-paclitaxel + GEM	$358,067/LY	$547,480/QALY

GEM indicates gemcitabine; ICER, incremental cost-effectiveness ratio; ICUR, incremental cost-utility ratio; LY, life-year; QALY, quality-adjusted life-year.

A 3-stage Markov analysis (PFS, progressed disease, and death) found that FOLFIRINOX was the most expensive regimen at an annual cost of $83,835, followed by nab-paclitaxel + GEM at $54,842. However, both yielded the highest nominal gains in life-years and QOL years compared with GEM monotherapy or GEM combined with cisplatin, oxaliplatin, or capecitabine.[19] An analysis of survival gains in patients with metastatic pancreatic cancer after the introduction of GEM, FOLFIRINOX, and nab-paclitaxel + GEM found that the cumulative value of survival gains attributable to GEM and nab-paclitaxel + GEM would exceed the cost of therapy by up to $47.6 billion and $39 billion, respectively, for patients with metastatic pancreatic cancer diagnosed in 2015 or later, whereas the lifetime value of survival gains in patients who can tolerate the FOLFIRINOX regimen would reach up to $26.3 billion.[20]

Targeted Therapies and Immunotherapies

Immunotherapy has not yet proven to be beneficial in pancreatic cancer. A unique tumor microenvironment, low levels of tumor-infiltrating T lymphocytes, and lower levels of antigens to target allow pancreatic cancer to be resistant to immunotherapy. Studies to date with single-agent immunotherapy have not been successful; however, there are multiple clinical trials examining different combinations of immunotherapy agents. Thus, the potential exists for immunotherapy in some form to play a role in pancreatic cancer.[21]

The FDA approved pembrolizumab in 2017 for patients with advanced solid tumors that have microsatellite instability–high (MSI-H) or mismatch repair–deficient (dMMR) markers that have progressed following prior treatment and have no satisfactory alternative treatment options.[22,23] Although this represents a small fraction of patients with pancreatic cancer, the potential exists for immunotherapy to play a role in pancreatic cancer.[24] To date, there are no published studies on the cost-effectiveness of immunotherapy in the pancreatic cancer setting.

The only targeted agent shown to be effective in the small number of EGFR-positive tumors is erlotinib, and, even though there was a survival advantage when erlotinib was combined with GEM, the benefit was actually small, suggesting a subset of patient benefit.[25] One study evaluated the budget impact of adding erlotinib to GEM for the treatment of locally advanced, nonresectable, or metastatic pancreatic cancer in a hypothetical model of 43 newly diagnosed patients in a 500,000-member managed care plan. The model estimated that 56% of the patients would be treated with GEM alone and 40% with combination therapy for 15.7 weeks per patient. The expected 1-year cost of $466,700 in the combination group was compared with $346,700 in the GEM-only group (2006 USD) translated to $0.020 PMPM.[26]

Cost-Containment Approaches for Managed Care

Specialty drugs are now the largest cost driver in pharmaceuticals. By 2020, they are estimated to account for half of total drug spending in the United States, although just 1% to 2% of Americans use them. In 2015, the average annual cost of treatment with a single specialty drug was $52,486, which was higher than the median wage and nearly as high as median income in 2016.[27] Targeted and immunotherapy cancer treatments are responsible for two-thirds of the increase in oncology costs between 2011 and 2016, and they now account for more than 43% of total pharmaceutical spending in the United States, or $50.7 billion in 2017.[28]

In a survey of payers representing 76 million commercially covered lives, 71% of respondents reported that managing oncology drugs and services is their top challenge.[29] A survey of 299 benefit leaders representing employers of an estimated 15.9 million covered lives found that 61% considered management of specialty drug costs as the number-1 priority.[27] Payers have implemented many approaches to managing high-cost drugs. Although treatments for pancreatic cancer are not currently a focus of many of these types of controls, if specialty drugs ever show efficacy, many of these approaches may be used. Some commonly used cost-control methods include:

- **Utilization and clinical management.** A recent analysis of 3417 health plan decisions related to specialty drugs found that 73.2% used step edits to restrict usage, 31.2% prescriber restrictions, and 16% patient subgroup restrictions.[30] Nearly all health plans have a prior authorization program in place for specialty drugs.[29] Prior authorization for chemotherapy is a very common practice for pancreatic cancer.
- **Site-of-care programs.** In the past few years, there has been a significant jump in the number of injections or infusions administered in hospital-owned sites, which costs significantly more than drugs administered in physician offices.[31] However, when acuity is adjusted, the cost differences may not be as many as perceived.[32] This perceived increase in cost has triggered a backlash among payers in the form of site-of-care programs, with a 135% increase in the number of health plans implementing these programs since 2013.[29,33] One payer estimated savings of up to $1.7 billion annually if site-of-care programs were employed nationally.[34] In oncology, this is still an uncommon practice; however, payers in regional areas have started discussions around this type of control, and it is anticipated that this approach may increase in cancer care over time.
- **Guidelines and clinical pathways.** In 2017, one-third of payers reported plans to improve their use of evidence-based guidelines in oncology, and 84% said they planned to partner with oncologists to develop oncology clinical pathways.[29]
- **Benefit design and cost sharing.** Whether to cover specialty drugs under the medical or pharmacy benefit affects member cost sharing and, thus, overall costs to the plan. To date, about 64% of plans require cost sharing for specialty drugs covered under the medical benefit as well as cost sharing for the physician visit.[29]
- **Partial-fill programs.** These programs are designed to reduce waste by providing a "trial" period to determine the effectiveness

and tolerance of oral chemotherapy. More than half (58%) of plans report using partial-fill programs for at least 1 specialty drug in 2017, up from 45% in 2016; 88% of those who did not use one for oncology drugs planned to implement one in 2018.[29] Currently, this type of program will have minimal impact on pancreatic cancer; however, if an oral agent eventually shows efficacy, it may become a possible cost-containment approach.

- **Network management and reimbursement**. These approaches include using average wholesale price for specialty pharmacy reimbursement, requiring National Drug Code numbers when nonspecific J-codes are used to bill under the medical benefit, negotiating with outpatient hospitals for shared 340B savings, and implementing episode-of-care or bundled payment programs similar to the Oncology Care Model (OCM) described below.[29]
- **Requiring the use of a specialty pharmacy.** Specialty pharmacies can improve outcomes while reducing the cost of expensive drugs.[35] In the Serono EMD survey, 68% of plans said specialty pharmacies offered the most competitive pricing on specialty drugs. This practice is increasing for injectable drugs; however, most insitutions are trying to resist the practice of "white bagging" at this time.[29]

More novel approaches include:

- **Indication-specific pricing**, an approach under which rebates and discounts are based on the benefits of the therapy for the indicated cancer.[36]
- **Preferred formulary placement** for reduced price when there are 1 or more drugs with the same indication.[37]
- **Annuity payments** for which the manufacturer is reimbursed over time rather than a one-time cost, with payments possibly tied to outcomes.[38]
- **Outcome-based payments**, in which rebates and discounts, even payment for the drug itself, are tied to clinical outcomes.[36,38]
- **Expanded risk pools** similar to the Medicare program for end-stage renal dialysis.[38]

However, all have significant downsides that limit their utility.[38]

Improving Outcomes and Reducing Costs

Although payers have numerous tools available to reduce the cost and utilization of specialty drugs, it is also important that they identify opportunities to reduce the overall costs of pancreatic cancer and improve patient quality of care and quality of life. Several possibilities are described here.

The Oncology Care Model

The OCM is a voluntary 5-year initiative from the Centers for Medicare & Medicaid Services (CMS). Participating physicians receive a monthly case management fee for every 6-month period a patient is under active treatment, and they are eligible for bonuses for meeting certain cost/quality metrics. The goal is to incentivize oncologists to more effectively manage and coordinate care for patients with cancer, lower the total cost of care, and improve care for beneficiaries during treatment episodes. The program began in 2016, and, as of May 2018, had 184 participating practices, including more than 6500 practitioners, as well as 13 commercial payers. Together, the practices delivered care to 1 of 4 Medicare beneficiaries with cancer, including nearly one-third of patients with pancreatic cancer.[39-42]

Evaluations of the program to date demonstrate some cost savings and outcome improvements. Consulting company Avalere found lower-than-predicted episode costs for most cancers, including pancreatic cancer, during the OCM pilot period.[43]

Oncology Hematology Care, a large practice in Cincinnati, Ohio, reported on its experience with several initiatives added in anticipation of OCM. These included a phone triage unit, after-hours and weekend calls, a weekend urgent care, and mandatory patient education for those receiving new treatments. In the year after implementing the program, the practice reduced acute care admissions by 16%, including unplanned readmissions within 30 days of discharge, resulting in Medicare savings of $3.19 million. At the same time, patient satisfaction survey scores improved.[44] Health plans that participate in OCM or develop similar programs for oncologists could reduce the costs of care for patients with pancreatic cancer as well as improve outcomes.

End-of-Life Care

About 25% of Medicare costs are spent in the last year of life, with 10% of the entire Medicare budget paying for care in just the last month.[45] In many instances, the type of care provided in the last 6 months of life, including chemotherapy, worsens the QOL in patients with good performance status and provides no benefit to those with poor performance status.[46]

One study of 3825 patients with stage IV pancreatic cancer aged 66 years or older found that chemotherapy use in the last 30 days of life led to substantially higher rates of hospital admissions (45% vs 29.2%; $P < .001$), ED visits (41.3% vs 27.2%; $P < .001$), and hospital-based deaths (14.2% vs 9.1%; $P < .001$) than those who did not receive chemotherapy. In addition, it resulted in a 50% increase in patient out-of-pocket costs ($1311 vs $841; $P < .001$).[46]

Palliative care and hospice can improve QOL, extend life, and, some studies show, reduce costs.[46-51] Indeed, guidelines recommend that patients with pancreatic cancer be referred to palliative care early in their diagnosis, whereas Medicare pays for hospice care once a patient has a life expectancy of 6 months or less.[39-41,52]

A recent analysis of 72,205 patients with pancreatic cancer found that just 4.1% received palliative care. Of these patients, 73% received care in the last 30 days of life and just 11% received care at least 12 weeks before death. Although those receiving palliative care incurred

higher healthcare costs than those who did not, the authors suggested that receiving care earlier could mitigate the additional costs, as shown in other studies.[53] Similarly, patients tend to enter hospice very late in the disease course. A recent study found that, although half of Medicare patients were receiving hospice services in 2015 when they died, just 7.7% had received services for 3 days or fewer.[54]

One barrier appears to be physician reluctance to discuss advanced planning with patients who have been newly diagnosed with metastatic cancer. One survey of 490 oncologists (response rate, 57%) found that just 34% would discuss prognosis, 14% hospice, 9.8% site of death, and 4.2% do-not-resuscitate status at time of diagnosis.[55] Such discussions, however, can reduce the use of acute care at the end of life, which could not only improve quality of life but also lower healthcare costs.[56] In 2016, the CMS released new codes allowing billing for such conversations, which advocates hope will encourage greater communication around end-of-life issues between physicians and patients.[39-41] Health plans may wish to provide opportunities and education to encourage physicians to initiate advanced planning discussions with their patients and consider earlier use of palliative and hospice care where appropriate.

Screening

As noted earlier, patients with metastatic or advanced pancreatic cancer incur much higher costs than those diagnosed earlier in the disease. Earlier diagnosis through screening, when the cancer is more likely to respond to treatment, offers an opportunity to improve outcomes and reduce costs.

A meta-analysis of 19 prospective cohort studies of 7085 asymptomatic adults at high risk of pancreatic cancer (lifetime risk >5%, including genetic-associated conditions) found an overall diagnostic yield of 0.74 (95% CI, 0.33-1.14) for high-risk pancreatic lesions, regardless of whether patients were screened with endoscopic ultrasound (EUS) or magnetic resonance imaging. The authors concluded that 135 patients would need to be screened to identify 1 patient with a high-risk lesion, and between 253 and 281 patients screened to prevent 1 death from pancreatic cancer. This estimate is similar to low-dose computed tomography scan for lung cancer in smokers and lower than that for mammography or hemoccult in stool screening.[57] The ideal early screening method would be a biomarker that would not only detect early-stage disease but would also provide prognostic information and distinguish benign from malignant lesions.

Ghatnekar et al developed a model based on the Swedish healthcare system to test the cost-effectiveness of screening older patients with newly diagnosed diabetes (a risk factor for pancreatic cancer) versus taking a wait-and-see approach using a proteomic test based on a serum biomarker signature. The model demonstrated a quality-adjusted life-year gained (ICER) of $15,370, which would be considered cost-effective in the United States.[58]

An analysis of the use of EUS screening for pancreatic dysplasia in a hypothetical cohort of 50-year-old commercially insured patients with a familial history of pancreatic cancer also found that it was cost-effective at an ICER of $16,885 per life-year saved (in 2003 USD), even considering treatment costs.[59] These, and similar studies demonstrating the cost-effectiveness of screening, have led to calls for the US Preventive Services Task Force to reevaluate its pancreatic cancer screening guidelines, which currently have a "D" rating.[60,61] Indeed, the task force has begun updating its 2004 guidelines and published a draft research plan in 2017.[62] Payers may want to consider covering screening for high-risk individuals, which could lead to earlier detection of pancreatic cancer and mitigate the need for higher-cost treatments in the late stages when the cancer is typically diagnosed.

Conclusions

Pancreatic cancer remains a cancer with one of the highest mortality rates, with less than a 10% 5-year survival rate after diagnosis. Few patients qualify for curative therapy, and existing chemotherapies add just months to OS. New targeted therapies and immunotherapies under investigation will likely transform the management of this disease, albeit at costs exceeding $100,000 per year.

The rising incidence of pancreatic cancer, its current economic burden, and the anticipated arrival of expensive targeted therapies and immunotherapies places increased pressure on payers to identify opportunities to improve outcomes for patients as well as reduce costs. Numerous options are available, ranging from restrictive policies, such as prior authorization, step edits, and partial-fill policies, to novel contracting approaches including outcomes-based reimbursement, annuity payments, and systemic changes, such as screening programs and bundled payments. It is important that health plans, employers, and public payers develop policies now to prepare for the anticipated changes. ■

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