HHS Public Access

Author manuscript

J Surg Oncol. Author manuscript; available in PMC 2018 March 26.

Published in final edited form as:

J Surg Oncol. 2016 September ; 114(3): 323–328. doi:10.1002/jso.24333.

The Impending Financial Healthcare Burden and Ethical Dilemma of Systemic Therapy in Metastatic Cancer

Muhammad Kashif Riaz, MD[1], **Susan Bal, MD**[1], and **Trisha Wise-Draper, MD, PhD**[2,*]

[1]Division of Hematology/Oncology, University of Cincinnati Medical Center, Cincinnati, Ohio

[2]Assistant Professor of Medicine, Division of Hematology/Oncology, Head and Neck Oncology/Experimental Therapeutics, Associate Hematology/Oncology Fellowship Director, University of Cincinnati Cancer Institute, Cincinnati, Ohio

Abstract

Metastatic cancer remains a devastating disease that threatens to disrupt entire family structures creating economic and psychosocial stress. Fortunately, great strides have resulted in improved therapies over the years but at a huge social-economic cost. The economic burden has risen greatly and carries with it new ethical concerns when deciding treatment. Here, we discuss the financial and ethical challenges that oncologists and their patients face in the era of novel treatment strategies.

Keywords

cost effectiveness; chemotherapy; metastatic cancer

INTRODUCTION

In 2016, an estimated 1,685,210 new cancer cases will be diagnosed and 595,690 people will die, which translates to about 1,630 cancer related deaths per day [1]. Most patients develop metastatic cancer during the course of their disease, which is incurable in almost all cases. However, over the past few decades important and significant strides have transpired in understanding, preventing, and treating metastatic cancer. Advances in clinical research and innovation have led to new therapies resulting in longer patient survival and improved quality of life. From conventional chemotherapy, we have progressed to targeted therapies and biologics, which often carry less toxicity and a more personalized approach to each patient. Recently, the exciting development of immunotherapy has once again whetted the desire to conquer the long fought battle against cancer.

*Correspondence to: Trisha Wise-Draper, MD, PhD, Division of Hematology/Oncology, Head and Neck Oncology/Experimental Therapeutics, University of Cincinnati Cancer Institute, Cincinnati, Vontz Center for Molecular Studies, Room 1304, 3125 Eden Avenue, ML 0562, Cincinnati 45267-0562, OH. Fax: (513) 558-6703. wiseth@ucmail.uc.edu.

Conflict of interest: All authors indicated no potential conflicts of interest.

DISCLAIMER

The pricing data of the drugs discussed above is representative of average whole sale price (AWP). It should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions.

Novel anti-cancer drugs have entered the market at a swift pace in the last few years. 2014 was a year of significant progress, in which Food and Drug Administration (FDA) approved nine new drugs, and added 10 new indications to existing drug labels. This was surpassed in 2015, which saw an unprecedented approval of 17 new drugs (six in 1 month) and 16 new drug indications for the treatment of cancer [2]. As the research boosts and technology refines, novel drug discoveries are expected to soar significantly in coming years.

Undoubtedly, these scientific advancements have brought us closer to making significant strides in treating, and even in some select cases, curing metastatic cancer. However, the latter has led us into a quagmire of uncontrolled cost and healthcare expenditures. 2015 was the first year to have healthcare spending reach $10,000 per person and national health care expenditures to hit $3.207 trillion (projected data) [3,4]. To put this into perspective, NASA spent $2.5 billion to send rover “Curiosity” to Mars, and the cost of the first human mission to Mars is estimated to cost around $100billion [5]. Health spending is projected to grow at an average rate of 5.8% per year and health share of gross domestic product (GDP) is expected to rise to nearly 20% by 2024 [4]. According to a recent study, cancer care expenditures are projected to reach $173 billion in the U.S. by 2020 [6]. The prices of patented cancer drugs since 2000 have vastly increased from $10,000 per year to $100,000 per year [7]. These extraordinary costs have translated to crippling financial hardships and mountains of debt for average income families.

INTERVENTIONS AND CLINICAL EQUIPOISE

As promising as they may seem, hapless reality is that many new interventions, such as biologics and targeted therapies, produce relatively small gains in life expectancy or quality of life in relation to existing treatments. There are many examples of clinical equipoise regarding various treatment strategies, especially when it comes to the metastatic setting. Therefore, it has become crucial to understand the potential costs and benefits of each intervention and to determine whether these interventions provide a “good value for the money.” Consider the following examples:

In metastatic colorectal cancer, it is a common practice to screen the tumor for KRAS mutational status. Patients with KRAS wild-type tumor have an option of anti-Epidermal Growth Factor Receptor (anti-EGFR) therapy with either Cetuximab or Panitumumab. These antibodies are usually used with a chemotherapy backbone but there is no consensus of using one over the other, and is usually left to the discretion of the treating physician [8]. However, if cost is taken into account, Panitumumab is more than twice as expensive as Cetuximab, but with similar efficacy and toxicity profiles.

Sandler et al. [9] reported a phase III trial determining the role of Bevacizumab in non-squamous non-small cell lung cancer. One arm received Carboplatin and Paclitaxel while the other arm received Carboplatin and Paclitaxel in addition to Bevacizumab. While the results favored the Bevacizumab containing arm, the overall survival advantage was modest resulting in a 2 month benefit. This was at the expense of increased treatment related deaths and a large price tag of Bevacizumab of about $8,900 per cycle.

Similarly, the EXTREME trial [10] investigated the efficacy of cetuximab plus platinum-based chemotherapy as first-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck. Investigators concluded that adding cetuximab to platinum-based chemotherapy significantly prolonged the median overall survival from 7.4 months in the chemotherapy-alone group, to 10.1 months in the group that received chemotherapy plus cetuximab. Around the same time a European trial, GORTEC 2008–03 [11] was ongoing evaluating the efficacy and safety of cetuximab, docetaxel, and cisplatin combination in a similar patient population with recurrent or metastatic squamous-cell carcinoma of the head and neck. The preliminary results reported in American Society of Clinical Oncology (ASCO) meeting were encouraging in favor of this combination. Note that these two trials are very similar with the same biological therapy (Cetuximab) and only slightly different chemotherapy. However, when cost is considered, Docetaxel is much more expensive than flurouracil. These trials established the role of anti-EGFR therapy in head and neck cancer and led to another study, the SPECTRUM trial [12] looking at the role of panitumumab, a much more expensive alternative to cetuximab as mentioned above in the colorectal cancer example. Panitumumab showed improvement in progression free survival but failed to show any overall survival advantage.

These few examples of many highlight the ambiguity in choosing one regimen over another. Clinically any of these treatment options would be perfectly appropriate because they are FDA approved and show similar efficacy with slight variations in toxicity profiles. But when analyzed closely, the bold fiscal differences between various trials become more vivid and hence, raises the question of cost effectiveness. This argument becomes even more relevant in the era of rising healthcare costs and calls for standardized guidelines, which would not only look into clinical benefits, but would also take into account the economic impact.

QUALITY OF LIFE CONSIDERATIONS AND COST OF THERAPY

With the advancement in oncologic care and the development of innovative therapies, patients often have multiple treatment options presented to them. In many cancers such as breast, colon, and multiple myeloma, several lines of therapies are offered, albeit with different levels of success. Since metastatic cancer is usually incurable, and chemotherapy is often the only possible treatment modality, drug toxicity becomes a major consideration. This has heightened awareness about the importance of evaluating the impact of treatment on patient's quality of life (QoL). QoL is a multidimensional concept and WHO defines it as "individual perception of life, values, objectives, standards, and interests in the framework of culture." [13] QoL is increasingly being used as a primary outcome measure in studies to evaluate the effectiveness of treatment, and in the palliative setting these outcomes are paramount. Poor QoL during treatment may affect a patient's ability or willingness to complete therapy, and affect compliance. Therefore, QoL considerations have affected the choice of treatment and also indirectly impacted the cost of therapy. Some of the major QoL issues are discussed below:

Neuropathy

Chemotherapy induced peripheral neuropathy is a major dose limiting toxicity of platinums, taxanes, and vinca alkaloids. Symptoms mainly consist of painful sensory impairment but may also affect motor functions, and the autonomic nervous system, resulting in major QoL implications. Neuropathy may affect activities of daily living such as buttoning shirts, signing one's name or typing on a computer as well as problems with standing, walking, or climbing stairs. Since there are no effective treatment options, every effort is made to prevent the development of symptoms, which may require use of alternate chemotherapy agents. A phase III trial compared nab-paclitaxel with paclitaxel in combination with carboplatin as a first-line treatment for advanced non-small cell lung cancer and found that nab-paclitaxel resulted in reduced rates of neuropathy [14]. However, nab-paclitaxel is about 15 times more expensive then paclitaxel. On the other hand, average healthcare costs for caring for chemotherapy induced neuropathy patients were $17,344 higher than controls [15], suggesting that the cost of modified chemotherapy may be justified in some cases.

Neutropenia

Neutropenia is another common side effect of cytotoxic chemotherapy, which may lead to febrile neutropenia and cause life threatening infections. It not only causes delays and interruptions in the chemotherapy schedule, which may be detrimental in a curative setting, but also adversely affects QoL. Patients may experience various QoL issues such as avoiding crowds, consuming neutropenic diets, routinely monitoring fever, and in severe cases, hospitalization, time off of work, isolation from friends and family etc. Neutropenia also has a major economic impact. A large retrospective study identified 26,628 hospitalizations with febrile neutropenia among breast cancer patients from 2009 to 2011. Mean length of hospital stay was 5.7 days and the mean cost of hospitalization was found to be $37,087 [16]. Therefore, it is imperative to prevent neutropenia from both a clinical and economic perspective. This requires either change in chemotherapy or use of growth factors such as pegfilgrastim, which in itself carries a significant cost of $6,186 per injection.

There are many other QoL implications which dictate the choice of chemotherapy and sometimes drive the cost higher or lower. For example some patients lack the means of transport and prefer oral chemotherapy instead of injectable agents requiring a change in treatment to a more expensive alternate, like ixazomib instead of bortezomib, or capecitabine in place of 5-flurouracil. Similarly, alopecia can be a major QoL issue, which sometimes affects the choice of therapy. There is a natural compulsion to offer palliative chemotherapy for improving QoL in patients with end-stage cancer. Prigerson and colleagues [17], however, found that the QoL near death in patients with end-stage cancer is not improved, and can actually be harmed, by chemotherapy use even in patients with good performance status.

All these issues of quality of life and interventions with clinical equipoise are valid but still do not explain trillions of dollars spent on health care in the United States. And ironically, when compared to European countries, healthcare outcomes are not better even after a significantly higher economic cost. Thus, urgent revision of policies and focus on cost effectiveness is required.

VALUE OF EACH INTERVENTION AND POLICY IMPLICATIONS

In 2007, American Society of Clinical Oncology (ASCO) took on a challenge to wrestle the dilemma of healthcare cost by creating the Cost of Care Task Force. The task force established principles and provided recommendations such as promoting adherence to evidence-based medicine, commitment to quality improvement, and establishing clinically meaningful outcomes for clinical trials [18]. But clearly, this herculean task cannot be done by one organization or singular society. Everyone must be in agreement including researchers, FDA, professional societies, oncologists, and even patients, before a change in the trend is expected.

Pharmaceuticals and FDA

There is no question that it takes a tremendous amount of time and money to develop new innovative drugs. The estimated average cost of bringing a new drug to the market is around $2.8 billion and takes about 10–15 years of research and development [19]. To cover these costs and to ensure funding for future research and growth, FDA provides exclusive marketing rights for about 11.5 years [20]. Unfortunately, some drug companies' demand unjust value for their product, like seen with a non-cancer drug, Daraprim [21], when the price was increased overnight by 5,000% resulting in strong criticism. A similar incident was reported by Bach et al. [22] who compared two biologics, ziv-aflibercept and bevacizumab for the treatment of metastatic colorectal cancer. It was noted that ziv-aflibercept had similar efficacy but for double the price of bevacizumab. After his review, the drug company manufacturing ziv-aflibercept immediately revised the price and reduced it by 50%.

Not only do these incidents damage veracity of the pharmaceutical companies, but also raises the question of how many artificially elevated prices go unnoticed and therefore, highlights the importance of professional criticism and analysis of cost effectiveness of new drugs.

The FDA approves a drug on the bases of its safety and efficacy and not the cost. And by-law, Medicare must cover every drug, which is approved by the FDA. Therefore, indirectly, the FDA acts as a rate limiting step and has an important role in controlling drug costs. Studies with only marginal benefits should be scrutinized more closely and investigators should be encouraged to power trials for more meaningful benefits. The most commonly cited study of Moore et al. [23] is an excellent example, in which gemcitabine was compared with gemcitabine plus Erlotinib for metastatic pancreatic cancer. The survival advantage was merely of 10 days and the average incremental cost of adding Erlotinib was $15,194 per patient [24]. Another interesting scenario is an approval of the immunotherapy, Nivolumab for metastatic melanoma. After the initial induction phase, FDA has approved it for maintenance therapy every 2 weeks until disease progression or unacceptable toxicity [25]. Because immunotherapy has shown impressive sustained long term responses in some patients, this raises questions about the benefit of prolonged maintenance therapy in these patients. Does it add anything or just subject patients to pharmacologic and economic toxicity for years?

Clinical Versus Statistical Response

Although, statistically the *P*-value of <0.05 is "significant," in reality it may have marginal "biological" significance. This was seen in a trial mentioned earlier, which evaluated Erlotinib in metastatic pancreatic cancer and found only a 10 day survival advantage. Similarly, recently approved epidermal growth factor receptor antagonist, Necitumumab in combination with chemotherapy for metastatic squamous cell lung cancer showed survival advantage of only 48 days when compared to chemotherapy alone [26]. This survival benefit was at the expense of considerable side effects, and a price tag of about $10,000/cycle. Hence, statistical information should be inferred carefully in the context of clinical application.

This, then leads to another complex question of what should be considered a "significant" survival advantage? What benefit does a drug need to deliver in order to be considered a new standard of care? There are no easy answers, but Richard Schilsky from ASCO [27] has made suggestions in an effort to create meaningful clinical outcomes, and thus liberating from reliance on *P* values. He suggested a minimal meaningful incremental improvement in Hazard ratio of <0.8 and median overall survival improvement of 2.5–6 months. These recommendations can serve as a benchmark for clinical trials and would also filter out studies with very modest benefits.

Study Designs and Pharmacokinetics

Investigators should also pay attention to pharmacokinetics of the drugs under investigation. For example, castrate resistant metastatic prostate cancer is usually treated with Abiraterone. The prescribing instructions are to administer Abiraterone on an empty stomach because food increases its absorption and can lead to higher serum concentrations. But what about decreasing the dose and asking the patients to take it with food? It may be safer and just as effective. Taking less pills will appeal to patients, increase compliance and considerably cut the cost. This was investigated in a small retrospective analysis of abiraterone administration with food, and its effect on PSA in castrate resistant prostate cancer patients [28]. Interestingly, it was observed, that some patients had reversal of PSA progression, and a decline in testosterone levels when they took abiraterone with food. Since this was a small retrospective study, concrete conclusions cannot be drawn. A large prospective multicenter clinical trial is underway, which will answer this question and help define the correct dose [29].

Another common dichotomy seen between study trials and clinical practice is the issue of performance status. Most of the patients who are considered eligible for a clinical trial usually have a good functioning capacity, which is generally not the case in day-to-day practice. This is especially true in the metastatic setting where patients have already gone through multiple rounds of chemotherapy and have developed cumulative side effects. If the trials are not analyzed closely, use of these newly approved treatments not only increase the risks of side effects, but also causes undue financial burden because of lack of benefit. This concept was seen in the CORRECT study [30], which led to the approval of a multi-kinase inhibitor, regorafenib for the treatment of refractory metastatic colorectal cancer. Patients enrolled in the study had either Eastern Cooperative Oncology Group (ECOG) performance

status of 0 or 1, whereas in practice, by the time patients are started on regorafenib, they usually have ECOG 3 and therefore, fare poorly with further treatment. In fact, some investigators have looked into dose modifications of regorafenib to avoid side effects and therapy interruptions [31].

Role of Oncologists

Medical oncologists shoulder great responsibility, which cannot be relegated to others. Patients' main source of information and the primary contact are their oncologists. Therefore, the oncology community should be at the forefront guiding clinical trials and explaining the outcomes of research as well as efficacy of new drugs to the patients. The common perception that a "new" drug is a "better" drug, should be clarified by explaining that a statistical significance may not mean biological advantage. Many patients do not get cost information from their oncologists, and even if patients ask, most of the doctors are unaware of the information. This is a major issue, because without knowing the cost of a certain drug or intervention, informed decisions cannot be made and economic burden cannot be expected to lighten. The medical community should be encouraged to discuss pharmacoeconomics with patients. It would not be surprising to observe patients foregoing certain treatments after being informed regarding rather small benefits at the expense of a high copay. Many patients live on fixed incomes and may not have the means to bear high costs, especially when the benefits are miniscule. Some patients may choose spending their savings on fulfilling their final wishes rather than pharmaceutical bills. Patients may choose to spend quality time, however limited, with their loved ones and families rather than the possibility of admission to the hospital with chemotherapy complications. It is important to provide patients autonomy in making these end of life decisions. However, there will always be a population of patients who will choose additional therapy no matter the futility. Whether society should be held responsible to pay for futile therapy is yet another area of ethical concern.

Non-Pharmacological Therapies

It is easy to overlook that patient outcomes can sometimes be optimized by non-pharmacological means as well. A prospective study looking at the significance of exercise behavior and functional capacity in recurrent glioma patients, found median survival was 13.03 months for patients reporting <9 metabolic equivalent [MET]-hr/week relative to 21.84 months for those reporting ≥9MET-hr/week [32]. Similarly, another study looked at the impact of Yoga and reported a decrease in inflammatory markers in breast cancer patients [33]. Imagine if exercise or yoga were a "drug," would the society be willing to pay $10,000–20,000 per month for these interventions? These are small studies but something to ponder when discussing treatment with patients. In cases where there are no further treatment options, emphasis should be on optimizing quality of life.

QALY AND COST EFFECTIVENESS

Putting a monetary value on someone's life continues to be an area of controversy and debate. However, in an attempt to assess the extent of the benefits gained from various interventions in terms of quality of life and survival, the idea of quality adjusted life year

(QALY) was introduced. QALY takes into account both the quantity and quality of life lived. It is calculated by the amount of time spent in a particular health state weighted by the utility score given to that state; 1 year spent in “perfect health” is equal to 1 QALY, while 1 year spent in “poor health” is less than 1 QALY [34]. Incremental cost-effectiveness ratio (ICER), on the other hand, is the ratio between the difference in costs and the difference in benefits of two interventions [35].

Most developed countries have set a certain cost-per-QALY threshold, which indicates how much the payer is willing to pay to gain an additional QALY. If the ICER of an intervention is below that threshold, the intervention is considered cost-effective; that is, it provides excellent value for the money. Alternatively, treatments with ICERs greater than the threshold are typically viewed as poor use of resources. United Kingdom typically uses £30,000/QALY, Canada uses about $50,000/QALY and although, no such threshold exists in United States, most of the studies have used $50,000/QALY [36].

Unlike other countries, cost-effectiveness data are not utilized in the United States during the drug approval process [37] and thus, leads to approval of drugs with marginal benefits at an extremely high expense. This is explained in Table I, which provides some examples to help understand the magnitude of economic burden with various interventions. Note the sharp differences between ICERs of the novel therapies and the older regimen, FOLFOX, but with almost similar gains in overall survival benefit.

The use of QALYs as a standard metric for assessing drug efficacy and cost-effectiveness is not without controversy, and its use does not guarantee solution to all the economic issues we face today. Quality of life is subjective and may mean different assessments to different individuals and some may even value quantity more than quality, hence skewing the calculation. It does not take into account the age or disability of the patient or the impact on caregivers and family. Therefore, QALY should be used as a guide rather than a deciding factor when considering various interventions.

CONCLUSIONS

The current pricing system is unsustainable and not affordable for many patients. The skyrocketing costs are putting enormous financial pressure on the society, in which cancer is becoming more prevalent and chronic with the advent of newer therapies. Many field experts have written excellent analyses and reviews on cost effectiveness of chemotherapy but Kantarjian et al. [46] has taken it to a different level. He has created an online campaign to collect the signatures of 1 million cancer patients affected by high drug prices in an effort to ratchet up the pressure on the government to negotiate prices with pharmaceutical companies. Every article, every review, and every step taken to create awareness against this uncontrolled financial chaos is admirable. Slight glimpse of these efforts being fruitful were seen on the approval of Necitumumab for non-small cell lung cancer, when researchers suggested the price of Necitumumab even before it was marketed [47]. Finally, we must continue to make a collective effort to curtail soaring prices so that patients are served better, while acknowledging that health care resources are limited.

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TABLE I

The Table Demonstrates Several Examples of Cancer Drugs Compared to Standards Used in a Variety of Tumors

Intervention	Comparator	ICER/QALY	Disease	Overall survival (OS) benefit	References
Regorafenib	Best supportive care	$734,153	Colon cancer	1.4 months	Goldstein [38]
Bevacizumab	Paclitaxel	$745,000	Breast cancer	No OS benefit	Montero [39]
Cetuximab	FOLFOX + Bevacizumab	$122,610	Colon cancer	5.7 months	Shankaran [40]
Imatinib	Physician choice tyrosine kinase inhibitor	$227,136	Chronic myeloid leukemia	No OS benefit	Larson [41]
Erlotinib	Gemcitabine	$410,000	Pancreatic cancer	0.33 months	Miksad [42]
Vemurafenib	Dacarbazine	$353,993	Melanoma	3.9 months	Curl [43]
Ixazomib	Lenalidomide + Dexamethasone	$433,794	Multiple myeloma	Not available yet	Institute of Clinical and Economic Review [44]
FOLFOX	FOLFIRI	$65,170	Colorectal cancer	5 months	Tumeh [45]

Using ICER (Incremental cost-effectiveness ratio) divided by QALY (Quality adjusted life year) gives an estimated cost given the known benefit of therapy, with quality of life taken into account, of each intervention compared to the comparator. It has been proposed, that in order for a therapy to be beneficial, that the ICER cost be below the QALY. The examples provided highlight that this is not the case in many interventions and are in fact, not cost effective given the small benefit.