VIEWPOINT

Cancer Treatment: The Cost Factor

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ABSTRACT

Countries in the Caribbean region have expressed concern at the rising incidence of chronic non-communicable diseases. Cancer is one of these and the cost of treating patients with this has escalated in the recent past. In this paper, the author examines colon cancer and the cost of caring for patients with this. A viewpoint with regard to the reasons for the increased cost of care of patients with cancer is advanced. The factors contributing to the increasing costs are explored. Research epistemology and the role of the pharmaceutical industry are also explored. The need for consensus decision-making with regard to choice of agent/regime is emphasized, as is the need for a deliberate cost-benefit approach.

Keywords: Cancer treatment, cost-effectiveness, toxicity

El Tratamiento del Cáncer: El Factor de Costo

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RESUMEN

Los países de la región del Caribe han expresado su preocupación por la creciente incidencia de enfermedades crónicas no transmisibles. El cáncer es una de estas, y el costo del tratamiento de los pacientes con cáncer ha aumentado en los últimos años. En el presente trabajo, el autor examina el cáncer de colon, y el costo del cuidado de pacientes con esta dolencia. Se presenta un punto de vista con respecto a las razones del aumento del costo de la atención a pacientes con cáncer. Se exploran los factores que contribuyen a los costos crecientes. También se exploran la epistemología de la investigación y el papel de la industria farmacéutica. Se enfatiza la necesidad de tomar decisiones de consenso con respecto a la elección del agente/régimen, como es la necesidad de un enfoque deliberado de costo-beneficio.

Palabras claves: Tratamiento del cáncer, rentabilidad, toxicidad

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INTRODUCTION

Healthcare today is characterized by near insurmountable complexity at the bedside as much as within the administrative framework that organizes its delivery. The cost of care has been rising at a phenomenal rate because of advances in complex technologies allied to medical care, innovative therapeutics that include "targeted" treatment, biological therapies, modern rehabilitative and cutting-edge supportive care. Doctors now have to be equipped with their *Ipods, Iphones* and *Ipads* – gigabytes of best practice guidelines, evidence-based algorithms and bedside medical calculators. Added to the direct cost of care *eg* cost of consultations, procedures and drugs, are the many indirect ones *eg* job loss, absence from work, and the overarching "administrative costs" involved in coordinating, organizing and monitoring the quality of care. Indeed, medical expenditure has become a leading cause of individual bankruptcy in the

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United States of America (USA) – perhaps the biggest global *per caput* spender on healthcare.

Expenditure on oncology – the treatment of colorectal cancer

One of the areas in which complex issues converge in a mesmerizing interplay is in the specialty of oncology. The current approach to research on cancer therapy in terms of the comparative effectiveness of one intervention over the other is cause for some concern. Perhaps the best way to illustrate the variables involved as contributors to the increasing cost of healthcare is to use the concrete example of the care of patients with colorectal cancer.

The 'norm'

Logically, the natural history of untreated colorectal cancer must be the yardstick against which the efficacy of any form of intervention must be judged (1). In this regard, Stathopoulos reported that out of a cohort of 40 patients, 65% with histologically confirmed 'moderately well differentiated' tumour node metastasis (TNM) stage IV adenocarcinoma of the colon survived for one year with no treatment or intervention apart from surgery for the primary lesion; 25% of the same cohort had a two-year survival (2). Sometime before this, Wagner *et al*, reporting on 252 patients with histologically confirmed colon cancer and hepatic metastases (solitary and multiple unilobar liver metastases), found that they survived for 21 and 15 months, respectively with no treatment other than removal of the primary tumuor. More than 20% of their patients with a solitary metastasis in the liver reportedly survived more than three years (1).

In a similar vein, Stangl *et al*, reporting on a series of 484 patients who presented with histologically confirmed colon cancer and hepatic metastases and who were followed between 1990 and July 1993 or until death, documented six specific findings that were predictive of survival in the absence of any treatment other than removal of the primary tumour (3). In order of importance, these were:

- percentage of liver volume replaced by tumour
- grade of malignancy of the primary tumour
- the presence of extrahepatic diseases
- mesenteric lymph node involvement
- the level of carcinoembryonic antigen
- the patient's age

These researchers found that for those patients who exhibited up to 25% or more replacement of their liver volume by metastases, by combining these prognostic factors in different ways, they could create outcome algorithms which for different sub-groups showed median survival times that ranged between 3.8 and 21.3 months. Hence, studies of the natural history of colon cancer tell us that patients with this disease can sometimes live for up to almost two years without any form of treatment apart from excision of the primary lesion when they have advanced disease. Indeed, anecdotally, one of my own patients who had histologically confirmed moderately well differentiated rectal cancer, having refused any treatment including tumour resection, lived for seven years with her rectal cancer.

Drug expenditure for patients suffering with cancer has doubled in the USA between 1987 and 2005 (4). I am certain that this has been the experience in the Caribbean as well. One would think that among the factors that might have contributed to this would have been the greater number of people having cancer (increasing incidence) as well as their increasing survival (rising prevalence). While these considerations may play a part, the other issues that factor into the increased costs have been the availability of more expensive treatments, the tendency today for oncologists to be much more aggressive with treatment and the changes in the site of care – hospital *versus* clinic care (5). Research has shown that the increasing prevalence of this disease and not the cost of treatment per patient is the main driver of the overall increased cost of care (4). But is this the whole truth? Surely, the complexity of treatment administration as well as the supportive care required when some of the more toxic cocktails are used must be factored into the overall cost of care.

Expenditure on drugs used in oncology has been increasing at a disproportionately higher rate than for drugs used in other areas of healthcare (6). These increased costs have not been confined to the USA and other developed countries, but have spread to developing countries as well. There are many reasons for this phenomenal increase in the cost of pharmaceuticals. Certainly, the replacement of older proven therapies by newer ones, along with the use of more complex regimes and longer periods of treatment have all been implicated in the cause of the rising cost of care, particularly of cancer patients. However, there are less obvious factors that are of a political nature that must be factored into this cost escalation. Patent rights have been guarded far more zealously than the right to health. Patent rights that extend across international borders have facilitated monopoly pricing for therapeutic agents. Poorer countries therefore often find it difficult to purchase many of the newer drugs. The recent Agreement on Trade-Related Aspects of Intellectual Property Rights (or the TRIPs Agreement), an international trade arrangement devised largely by transnational corporations in developed countries that redounds to their own advantage, is but one example of the divisiveness with which third world countries have to come to terms, as such agreements often exacerbate pre-existing difficulties in accessing much needed pharmaceuticals. The evolution of these cross-border trade arrangements has no doubt been instrumental in contributing to the escalating cost of drugs to the benefit of share prices of the pharmaceutical manufacturers rather than that of the patients (Tables 1 and 2).

Do higher drug prices mean better clinical outcomes?

Between 1980 and the mid-1990s, fluorouracil was the mainstay in the chemotherapy of colorectal cancer. Regimens of 5-FU combined with either leucovorin or levamisole,

Table 1: Regimens established as superior to fluorouracil alone in advanced colorectal cancer

Regimen	Estimated drug cost for six months*	Comments
1. Fluorouracil, 425 mg/m^2 of BSA, plus leucovorin, 20 mg/m^2 both by rapid IV injections daily for 5 days every 4 to 5 weeks	$545	As compared with fluorouracil alone, results in significant improvement in survival, time to progression, regression rate and quality of life.
2. Fluorouracil, 370 mg/m^2 plus leucovorin, 200 mg/m^2 both by rapid IV injections daily for 5 days every 4 to 5 weeks	$4110	Therapeutically equivalent to regimen 1; no justification for increased cost.
3. Fluorouracil, 600 mg/m^2 plus leucovorin, 500 mg/m^2 both by rapid IV injections weekly for 6 weeks followed by 2 week rest and then repeated	$7005	Survival and regression rate equivalent to those with regimen 1; excessive hospitalization and drug costs.
4. Methotrexate, 200 mg/m^2 given in a 4-hour infusion; fluorouracil, 1100 mg/m^2 given by rapid IV injections at hour 7; and leucovorin, 14 mg/m^2 given orally beginning at hour 24 and repeated every six hours for 8 doses; repeated every 3 to 4 weeks	$1970	Survival and regression rate inferior to those with regimen 1; other regimens of this combination may be as effective but have not been compared with fluorouracil alone.

*Costs reflect average wholesale prices, according to the Red Book, for drugs required to treat a patient with 1.8 m^2 of body surface area. Actual costs may differ because of local retail pricing. Substantial savings may be possible through generic or consortium purchasing.

Table 2: Regimes established as superior to fluorouracil alone in advanced colorectal cancer

Regimen	Estimated cost for eight weeks	For six months
1. FOLFOX – leucovorin 5-FU, oxaliplatin	$12 000.00	$36 000.00
2. FOLFOX/bevacizumab	$21 000.00	$63 000.00
3. FOLFIRI – leucovorin 5-FU, irinotecan/cetuximab	$30 000.00	$90 000.00

while they may have been marginally less effective than today's combinations, afforded a better quality of life for the patient as there was far less systemic toxicity. Between 1996 and 2004, the US Food and Drug Administration (FDA) granted approval to five new agents *viz*: irinotecan (Camptosar – 1996), oxaliplatin (Eloxatin – 2002), capecitabine (Xeloda –1998), bevacizumab (Avastin – 2004) and cetuximab [Erbitux – 2004] (7) [Table 3].

Table 3: Chemotherapeutic agents used in the treatment of colon cancer

Agent	Classification	Trade name
Flourauracil	Antimetabolite (pyrimidine analog)	Adrucil
Capecitabine	Oral 5-FU analogue	Xeloda
Tegafur + Uracil	Combination of the 5-FU congener prodrug tegafur (tetrahydrofuranyl-5 -fluorouracil) and uracil (1:4)	
Irinotecan	Natural source (plant) derivative	Camptosar
Oxaliplatin	Alkylating agent	Eloxatin
Cetuximab	Monoclonal antibody; epidermal growth factor receptor (EGFR) inhibitor	Erbitux
Paniumumab	Monoclonal antibody; EGFR inhibitor	Vectibix
Bevacizumab	Monoclonal antibody; EGFR inhibitor	Avastin
Aflibercept	Vascular endothelial growth factor (VEGF) inhibitor	Zaltrap
Regorafenib	Tyrosine kinase inhibitor/VEGF inhibitor	Stivarga

The claim has been made that "better systemic therapy has considerably improved prognosis", since "without chemotherapy, the median duration of survival among patients with metastatic colorectal cancer was eight months"; with fluorouracil it was extended to 12 months, while the addition of irinotecan and oxaliplatin is said to have extended survival to 21 months (7). These claims deserve closer scrutiny not only because they are similar to the normative survival benchmarks discussed above in respect of "non-intervention", but because of their "looseness". Figueredo *et al*, in a meta-analysis of pooled studies, showed that following complete resection of stage II colon cancer (Dukes B2; *ie* associated 'high-risk' features), the additional use of chemotherapy combinations adds nothing to overall survival (8). Similarly, Roque I Figuls *et al*, in their own Cochrane review of second-line therapy, reported no advantage apart from a single study that is yet to be replicated (9). Even the use of radioactive beads in addition to chemotherapy has been found to have no effect in the way of improved survival in colorectal cancers with metastases (10).

Expensive and at times toxic cocktails offer only marginal benefit at near prohibitive cost. Table 1 reviews the cost of a few of the more popular regimes (11). Table 2 reviews costs for three of the more recent regimes (5). The US dollar amounts quoted are at 2012 prices. One would think that since health is not regarded as a human right by some, but is rather thought of as a commodity subject to market forces, that higher prices would be reserved for higher quality products. There is an obvious disconnect between the price signal and resource value. Added to this cost-benefit dissonance is the distressing reality that many of the phase II and phase III drug trials are being conducted as if they were marketing exercises. During the 1980s, researchers were independent of their sponsors. Pharmaceutical corporations are today involved in every aspect of research into their products. Clinical trials today are controlled by the pharma industry. Pfeizer, for instance, in one of their trials on sunitinib, had just one person in a multi-tiered research team who was not paid by them. Today, "Big Pharma" controls the research and has doctors on their payroll. They decide on the study design, control the raw data, analyse the data themselves and even pay private entities to actually write the papers. If that were not bad enough, top-level private sector corporate managers move through a "revolving door" to the FDA from "Big Pharma" and return to "Big Pharma" from the FDA.

DISCUSSION

Within this maze that we call oncology, which calls for knowledge-based lateral thinking in decision-making, one is confronted by yet another dilemma: that of the reductionist approach that is applied to cancer research epistemology. This approach defies the notion of biological individuality and proceeds to inform on "best practice" that is based on superficially-understood evidence. The gold standard of the randomized control trial (RCT) needs to be revised with a view to a new epistemology. The RCT advised the use of monoclonal antibodies in colon cancer; subsequent research advised that they be used only for a specific genomic group. Where biological specificity is recognized, it only serves to further drive up the cost of medical care with little commensurate benefit to the patient. The use of the monoclonal antibodies cetuximab and panitumumab is reserved exclusively for patients exhibiting 'wild type' kRAS polymorphism.

Expensive pre-treatment tests are therefore required. Why was *levamisole* abandoned? The medical community as a whole and particularly doctors in developing countries need to sit back and consciously and dispassionately "see" where the practice of medicine is going and assess the level of benefit that is accruing to the people we serve. There ought to be greater concern expressed in regard to the issues regarding the treatment of all forms of cancer. Decision-making in this regard has to be by hospital oncology board consensus and firmly based of cost-benefit scrutiny.

CONCLUSION

Systematic review of the literature would suggest that a rational approach to colon cancer needs to be better worked out. Far too much influence has been brought to bear on this issue by the intrusion of and subtle pressure from the pharmaceutical industry on this aspect of healthcare. There is a need to re-analyse raw data that pertain to several of the trials in which these data have been controlled by that industry. The need also exists to discontinue the dubious practice of allowing free access to the industry's hierarchy to the halls of power – primarily the FDA – as this practice lends itself to the perception that the fox is guarding the hen-house. An open revolving door causes the erosion of trust. The continuance of the present arrangement frustrates the practice of good healthcare and reduces the art of medicine to a self-serving pseudo-profession, as the good of the patient is replaced by what is best for the drug industry and the remuneration of the doctor.

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