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Economic Evaluations of Hematological Malignancies Compared with Solid Tumors

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Abstract

Introduction: Cancer care costs escalated with the introduction of novel therapies. Therefore, cancer–related Cost Utility Analyses (CUAs) are used to guide policy makers. Since numerous methods (criteria) exist to evaluate CUAs, we compared these criteria between CUAs of solid tumors and those of hematological malignancies.

Methods: A systemic MEDLINE search of English-language publications between 2001 and 2012 was performed. Strict inclusion criteria were limited to CUAs examining one single intervention and one single study comparator. Standard data of 66 variables, based on the Drummond criteria, were collected to review each CUA for clarity, completeness, and health economic methodological quality.

Results: Among 8,515 screened papers on Pubmed, 177 cancer-related CUAs (2%) were eligible. Solid tumors and hematological malignancies CUAs constituted 161(91%) and 16(9%). Among the standardized methods for evaluating CUAs, those of solid tumors reported more frequently the presentation of cost-effectiveness acceptability curve (p=0.02) and the use of threshold value to interpret study results (p=0.024) than those of hematological malignancies. Further, CUAs of solid tumors were more frequently multicenter-based (p=0.014); however, CUAs of hematological malignancies listed differential quality adjusted life year separately more frequently (p=0.02). Outcomes of CUAs of solid tumors were more frequently reported as significant (p=0.014).

Conclusions: CUAs of solid tumors abided more frequently with the standardized methods (criteria) than those of hematological malignancies, which may be due in part to their multiple study sites. CUAs of hematological malignancies may warrant more methodological standardization and incorporate more study sites.

Keywords: Cost effectiveness analysis; Cost utility analyses; Solid tumors; Hematological malignancies

Abbreviations: CEA: Cost Effectiveness Analysis; CUAs: Cost Utility Analyses; ICER: Incremental Cost Effectiveness Ratio; QALY: Quality-Adjusted Life Year

Introduction

The cost of cancer care has increased tremendously in the United States and worldwide [1]. Methods to evaluate the cost of cancer care in relation to the benefit it produces are called Cost Utility Analyses (CUAs). Many variables contribute to CUAs. For this purpose, cost-effectiveness acceptability curves were used to produce confidence intervals around Incremental Cost-Effectiveness Ratios (ICERs) [2,3]. Drummond and Jefferson [4] generated a list of 35 questions to evaluate the quality of CUAs and are now used to assess systematic reviews. These criteria allow differentiation between "good" CUAs and others. On the other hand, solid tumors are common but the effect of some of the treatments on longevity is sometimes measured in months from diagnosis while hematological malignancies are rare but are associated with the potential to result in significant prolongation of life expectancy [5]. Therefore, we aimed to compare CUAs of these two groups. Moreover, considering the society perspective, the economic burden varies considerably by each type of cancer [6,7]. Hence, an increased need was recently raised to examine cost by conducting CUAs [8-14]. The purpose of our paper is to compare methodologies used to study economic evaluations using two groups: solid tumors and hematological malignancies.

Methods

A systemic MEDLINE search by the keywords: CUAs and cancer of English-language manuscripts published between 2001 and 2012 was performed. Eligibility criteria consisted of including only CUAs that examined one single intervention and one single study comparator. For example, adding rituximab to fludarabine and cyclophosphamide for the treatment of previously untreated chronic lymphocytic leukemia [15]. Exclusion criteria included CUAs that examined more than one intervention, more than one comparator or more than one study population or type of malignancy. The study population was not limited by age; therefore, CUAs examining children, adult or geriatric populations were included. Research keywords included the following words: CUAs, cost-effectiveness analysis, malignancy, leukemia, lymphoma, myeloma, tumor, genitourinary, bladder, penile, renal, prostate, gastrointestinal, stomach, esophagus, colon, duodenum,

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small intestine, cecum, appendix, neuroendocrine, liver, pancreas, brain, head and neck, lung, mesothelioma, thymus, sarcoma and cancer. The number of patients was broken down by hematological malignancies or solid tumors and not by each type of cancer, as this was not the scope of our paper. Table 1 represents the workflow of the systematic approach examining all variables in each CUA. Selected CUAs incorporated studies patients of all ages and ethnic groups from the USA, Europe and developing countries. Based on the Drummond criteria [2], we examined the clarity, completeness, and health economic methodological quality of each CUA by collecting 66 variables [4]. Among the variables represented in our workflow, we examined whether CUAs performed univariate and multivariate sensitivity analyses, including the time horizon, the costs of each drug, and the transition probabilities. Additionally, we examined whether a Tornado graph (a graph to calculate the most favorable ICER by varying each parameter of interest) and a cost-effectiveness acceptability curve were used.

Pubmed ID
Journal
Date publication
CUA type
Intervention type
Prevention Stage
Study Theme Disease name: cancer type
Focus study name
Comparator name
Funding source
Clear Presentation of the Relevant Intervention
Clear Presentation of the Comparator
Clear Presentation of the Target Population
Time Horizon Incremental Analysis
Methods name
Total number of patients in the study
Number patients on focus study
Number patients on comparator study
Currency name of cost study
Total/ lifetime cost of focus study
Confidence Interval (CI) focus study cost lower value
Confidence Interval (CI) focus study cost upper value
Total/ lifetime cost of alternative study
Confidence Interval (CI) comparator cost lower value
Comparator lifetime cost
Confidence Interval (CI) comparator cost upper value
Incremental Cost per year of life gained- alternative
Confidence Interval (CI) /SE of comparator intervention (lower value)
Confidence Interval (CI) /SE of comparator intervention (upper value)
Incremental Cost per year of life gained- focus
Confidence Interval (CI) / Standard Error (SE) of Incremental Cost Ratio Lower Value-focus
Confidence Interval (CI) /SE of Incremental Cost Ratio Upper Value-focus
Confidence Interval (CI) /SE of Incremental Cost Ratio Lower Value-alternative
Confidence Interval (CI) /SE of Incremental Cost Ratio Upper Value-alternative
Quality-adjusted life year (QALY) unit for focus
Quality-adjusted life year (QALY) CI for focus lower value
Quality-adjusted life year (QALY) CI for focus upper value
Remaining QALY for alternative
CI for remaining QALY in alternative lower value
CI for remaining QALY in alternative upper value
Remaining QALY for treated
Calculated Cost utolity analysis (CUA)
CI/SE of CEA lower value
CI/SE of CEA upper value
Drug Administration Method
Drug Combinations
Type of therapy
Study Institution number
Pharmaceutical company number
Study Site
Cancer Type
Outcome
Perspective
Continent of study
Discounting
ICER (incremental cost effectiveness ratio)
Sensitivity Analysis
Tornado Graph included
High/Low limits Provided
Presentation of cost-effectiveness acceptability curve
Clinical trial based economic analysis
Use of Threshold Value to interpret study results

Table 1: A workflow of the systematic approach detailed examining all variables in each cost utility analysis.

Statistical Analysis

The data were reported as means, standard deviations, medians and inter-quartile ranges for continuous variables, and as frequencies and relative frequencies for categorical variables. Corresponding 95% confidence intervals were constructed when appropriate. The study variables were compared between the two groups (using the Chi Square test for categorical variables and either the ANOVA (Analysis of Variance) or Kruskal Wallis test for continuous variables. Statistical software SAS version 9.1.3 (SAS Institute, Inc., Cary, NC) was used for this analysis. The difference between the two groups was considered statistically significant if the p value was less than 0.05.

Results

After screening 8,515 published manuscripts on Pubmed, we identified 177 cancer-related CUAs (2%) that met our criteria. Consistent with the higher frequency of solid tumors compared with lymphoma, leukemia and myeloma [5], CUAs pertaining to solid tumors represented 91% of those studies. We compared the collected variables between solid tumors and hematological malignancies (Tables 2a and 2b). Our data reveal that CUAs of solid tumors reported more frequently the presentation of cost-effectiveness acceptability curve ($p=0.02$) and the use of threshold value to interpret study results ($p=0.024$) than their counterparts. In regards to the Quality-Adjusted Life Year (QALY) and the utility (numeric figure assigned for each particular health state) for that state over all the health states we found that CUAs of solid tumors were more frequently multicenter-based ($p=0.014$) and were more frequently reported as significant ($p=0.014$). On the other hand, CUAs of hematological malignancies listed more frequently differential QALYs separately ($p=0.02$).

Discussion

The cost of a drug is measured in monetary units while benefit is measured in health gain such as survival. However, quality of life is added to this formula. For example, if intervention A results in five

Characteristic	Hematological Malignancies	Solid Tumors	p-value of χ^2 test
Number of CUA	16	161	
The relevant intervention, %	93.75	90.68	0.6833
The comparator, %	100.0	87.58	0.1344
The target population, %	100.0	99.38	0.7519
Time horizon, %			
Lifetime	37.5	41.61	0.7498
Other	62.5	53.42	0.4867
Not stated	0.0	4.97	0.3615
Time horizon stated, %	100.0	95.03	0.3615
Study perspective, %			
Societal	25.0	27.85	0.8081
Health-care payer	75.0	72.15	0.8081
Discounting, %			
Costs only	18.75	12.34	0.4670
QALYs only	0	0.65	0.7465
Both costs and QALYs	50.0	54.55	0.7284
Not needed	6.25	19.48	0.1921
Any discounting, %	68.75	70.13	0.9087
Clinical trial based economic analysis, %	56.25	71.88	0.1915
Sensitivity analysis, %			
Univariate or multivariate	50.0	44.10	0.6507
Probabilistic	37.5	44.10	0.6116
Other/Unknown	6.25	7.45	0.8603
Not performed	6.25	4.35	0.7269
Any sensitivity analysis, %	93.75	95.65	0.7269
Presentation of cost-effectiveness acceptability curve, %	18.75	49.07	**0.0204**
Use of threshold value to interpret study results, %	56.25	80.50	**0.0249**

Table 2a: Characteristics of CUAs of hematological malignancies and solid tumors.

additional years of survival compared to no intervention with a quality of life of 0.5, than the intervention results in 5×0.5=2.5 QALYs. If, on the other hand, intervention B results in seven additional years of life compared to no additional intervention but at a quality of life of 0.25, then it confers 7×0.25=1.75 QALYs. Therefore, the additional benefit of intervention A over intervention B is 0.75 QALYs even though intervention B results in longer survival.

Another way to compare the two treatments is to calculate the ICER. For that we will need to add the monetary effect of each treatment. For example, intervention A would cost $10,000 per year while intervention B would cost $5,000 per year. In the above example, ICER equals 10,000-5,000/2.5-1.75=$6,666.67 per QUALY for intervention A compared with intervention B.

Calculation of costs is complicated; for example, one can calculate only the price of a drug. However, the societal effect of an intervention has to be taken into consideration as well. If we look at intervention A that requires the patient to return to the hospital three times per week compared to intervention B that requires the patient to return to the hospital only every two weeks, the effect of the each interventions can be significantly different, especially if both interventions require that the patient be escorted. The effect of the intervention on the companion in regards to loss of working days has to be taken into account when one considers cost. Another important factor is the time horizon, that is, how long the intervention is used. In the examples above, if intervention A is used for one year while intervention B is to be administered for the lifetime of the patient, it is clear that a difference in time horizon exists between the two matological malignancies are rare and represent a distinct group of cancer. In recent years, there have been a significant number of compounds approved for the treatment of these rare tumors. Those drugs impose a substantial financial burden in regards to the US and worldwide taxpayers [15,16]. Therefore, CUAs of novel therapies either in solid tumors or hematological malignancies are particularly important to delineate their additional cost and benefit. Hence, it is imperative to evaluate whether these CUAs are strictly conducted without any contamination of a financial bias. Moreover, it is essential that these studies follow rigorous scientific rules. Therefore, we for the most part, explored if any differences existed between CUAs of solid tumors and hematological malignancies. Based on the collected variables (defined in Table 1, 2a and 2b), we found that CUAs of solid tumors abided more frequently with the standardized methods (criteria) than those of hematological malignancies. This may have been due in part to the fact that these studies were conducted in multiple sites. On the other hand, CUAs of hematological malignancies may warrant more standardization of their methodologies and incorporating more study sites. While we are quite concerned how experts would evaluate methodologies of conducting CUAs, we noted an improvement in the percentage of studies that appropriately report a calculated ICER [16] because reporting a calculated ICER is an established criterion that the CUA has been appropriately conducted. Moreover, a probabilistic sensitivity analysis has been more frequently reported in recent CUAs, again denoting an improvement in the quality of these studies. Nonetheless, while reviewing the literature we found that many of these studies still did not report time horizon. Other important deficiencies involved the quality of reporting the discount costs (the discount rate is the rate that needs to be discounted at future date and to estimate accurately the net present value of cost and benefits) or the QALYs. Another major concern was the publication bias that tackles publishing CUAs in peer-reviewed journals that are experienced in reporting such studies to the public domain [17]. As faculty in academic malignant hematology, we are concerned about the quality of CUAs in this field. After reviewing carefully the literature, we believe that applying standardized methods [2] for evaluating CUAs methodologies is essential. There are numerous ways to assess these methodologies; however, we think that the Drummond criteria may be quite sufficient to lead to an accurate reporting of CUAs [4].

Characteristic	Hematological Malignancies	Solid Tumors	p-value of χ^2test
Number of CEA	16	161	
Funding source, %			
Industry/Non-Industry vs. Non-Industry	72.73	52.76	0.2021
Study Institution Number, %			
Single site	73.33	40.65	**0.0148**
More than one site	26.67	59.35	**0.0148**
Currency name, %			
USD	81.25	56.85	0.0593
Industry/ Industry &Non-Industry	62.50	44.93	0.3457
Euro	18.75	43.15	0.0593
Industry/ Industry &Non-Industry	100.0	60.87	0.1731
Outcome statistically significant, %	66.67	91.80	0.0149
ICER listed, %			
Base QALY listed	41.67	41.77	0.9943
Cost listed separately	16.67	42.41	0.0800
Differential QALY listed separately	41.67	15.82	0.0236
Tornado Graph included, %	25.00	31.06	0.6158

Table 2b: Characteristics of CUAs of hematological malignancies and solid tumors.

At the end of our discussion, it is important to state that these deficiencies of CUAs were disconcerting, as they have equally been noted in solid tumors as well as hematological malignancies [4]. Additionally, we still think that more robust criteria must be carried to conduct these CUAs especially when considering newer therapies. In this area, we have noticed an obvious pressure from pharmaceutical industry to deviate the outcome in favor of their products.

Conclusion

CUAs of hematological malignancies when compared with those of solid tumors abided less frequently with the standardized methods (criteria) as well as they were conducted in fewer study sites. Therefore, economic evaluations of hematological malignancies may warrant applying strict criteria and incorporating more study centers. However, more validation in future prospective studies is needed.

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References

1. Tangka FK, Trogdon JG, Richardson LC, Howard D, Sabatino SA, et al. (2010) Cancer treatment cost in the United States: has the burden shifted over time? Cancer 116: 3477-3484.
2. vanHout BA, Al MJ, Gordon GS, Rutten FF (1994) Costs, effects and C/E-ratios alongside a clinical trial. Health Econ 3: 309-319.
3. Briggs A, Fenn P (1998) Confidence intervals or surfaces? Uncertainty on the cost-effectiveness plane. Health Econ 7: 723-740.
4. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL(2005) Methods for the economic evaluation of health care programmes. (3rdedn),Oxford: Oxford University Press,UK.
5. Siegel R, Naishadham D, Jemal A (2013) Cancer statistics, 2013. CA Cancer J Clin 63: 11-30.
6. Kasteng F, Sobocki P, Svedman C, Lundkvist J (2007) Economic evaluations of leukemia: a review of the literature. Int J Technol Assess Health Care 23: 43-53.
7. Kasteng F, Sobocki P, Svedman C, Lundkvist J (2007) Economic evaluations of leukemia: a review of the literature. Int J Technol Assess Health Care 23: 43-53.
8. Raftery J (2009) NICE and the challenge of cancer drugs. BMJ 338: b67.
9. Mason AR, Drummond MF (2009) Public funding of new cancer drugs: Is NICE getting nastier? Eur J Cancer 45: 1188-1192.
10. Rocchi A, Menon D, Verma S, Miller E (2008) The role of economic evidence in Canadian oncology reimbursement decision-making: to lambda and beyond. Value Health 11: 771-783.
11. Dalziel K, Segal L, Mortimer D (2008) Review of Australian health economic evaluation - 245 interventions: what can we say about cost effectiveness? Cost Eff Resour Alloc 6: 9.
12. Tengs TO (2004) Cost-effectiveness versus cost-utility analysis of interventions for cancer: does adjusting for health-related quality of life really matter? Value Health 7: 70-78.
13. Steinbrook R (2008) Saying no isn't NICE - the travails of Britain's National Institute for Health and Clinical Excellence. N Engl J Med 359: 1977-1981.
14. Van Lare JM, Conway PH, Sox HC (2010) Five next steps for a new national program for comparative-effectiveness research. N Engl J Med 362: 970-973.
15. Experts in Chronic Myeloid Leukemia (2013) The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts. Blood 121: 4439-4442.
16. Hornberger J, Reyes C, Shewade A, Lerner S, Friedmann M, et al. (2012) Cost-effectiveness of adding rituximab to fludarabine and cyclophosphamide for the treatment of previously untreated chronic lymphocytic leukemia. Leuk Lymphoma 53: 225-234.
17. Greenberg D, Earle C, Fang CH, Eldar-Lissai A, Neumann PJ (2010) When is cancer care cost-effective? A systematic overview of cost-utility analyses in oncology. J Natl Cancer Inst 102: 82-88.