

Grading methodology for costs and values of anti-cancer drugs; application in metastatic colorectal cancer

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Abstract

Background: The present study was prompted by the inability of patients to afford the costs and understand value issues of anticancer drugs. We postulated that society in the United States would be willing to pay 4-week costs (4wC) up to \$5,000 and reject >\$10,000.

Objectives: 1- Propose simplified methodology to grade costs, weigh values and apply in metastatic colorectal cancer (mCRC)

Methods: 4-week society costs (4wC) were graded A for up to \$5,000, B \$ >5,000 to \$7,500, C \$ >7,500 to \$10,000, D >\$10,000. Values defined as C/life-year gain (LYG) were graded from A100,000 to D >300,000. Relative values (RV) were calculated with reference to 100,000 QALY. $RV = 100,000/C/LYG$ for drugs with maintenance or improvement of quality of life (QoL).

Results: In 1st-line 4wC and grades of Bevacizumab (Bev) were \$4,620/A. In KRAS wild type Paninitumab (Pan) was \$8,233/C and Cetuximab (Cet) \$9,775/C. Values and grades were Bev 141,549/B, Pan 269,444/B and Cet 351,900/D. The corresponding RV were 0.71, 0.49 and 0.28. In 2nd-line Ramucirumab (Ram) 4wC were \$11,200/D, values 252,200/C and RV 0.20. In refractory disease Regorafenib (Reg) 4wC were \$12,500/D, values 321,429/D and deductible \$1,250 compared with TAS 102 \$12,890/D, values 257,800/C and deductible \$1,289. RV could not be ascertained for lack of immature and/or inconclusive QoL data.

Conclusions: Methodology to grade drug costs and values was feasible and user-friendly. In 1st-line mCRC Bev 4wC was affordable with grade A, higher than Pan and Cet. In later lines 4wC of Ram, TAS 102 and Reg were >\$10,000 with D rating. Their values could improve with use at earlier therapy lines.

Abbreviations: Adverse events (AEs), Average wholesale price (AWP), Average cost-effectiveness ratios (ACER), Bevacizumab (Bev), Cetuximab (Cet), Confidence Interval (CI), Cycle (cy), Epidermal growth factor receptor (EGFR), 5-Flourouracil (F), 4-week costs (4wC), Hazard Ratio (HR), Irinotecan (Ir), Intravenous (iv), Leukovorin (L), Metastatic colorectal cancer (mCRC), Milligram (mg), Month (m), Monthly cost (mCost), every (q), Monoclonal Antibodies (MABs), Oral (po), Oxaliplatin (Ox), Overall survival (OS), OS gain over control idays (OSg), Panitumumab (Pan), Quality of life (QoL), Ramucirumab (Ram), Regorafenib (Reg), Relative values (RV), Vascular endothelial growth factors (VEGF), Week (w), Wild type (WT), zif-aflibercept (Afl).

Introduction

Rising costs of anticancer drugs continue to raise serious concerns on approval, utilization affordability and adherence (1-4). Gaps of communications in cost and value issues seemed to exist between physicians and patients (5, 6). The American Society of Medical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) (7, 8) have recently emphasized the need to contain drug costs and improve values. The National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK) set limits on average cost-effectiveness ratios (ACER) of 20,000-30,000 pound per quality adjusted life-year (QALY), equivalent to 30,000-50,000 in US dollars. Generally considered acceptable are cost-effectiveness ratios of \$50,000 to \$150,000 per quality QALY. The methodology was recently described with built-in limits on C/LYG (9).

The objectives of the present investigation were:

- 1-Propose a simplified grading method to rate drug costs and facilitate communication between physicians and patients.
- 2- Limit the 4wC to \$10,000 and apply in metastatic colorectal cancer (mCRC).

Methods

Average wholesale 2015 drug prices and/or third-party payments in US\$ were utilized. Drugs with documented overall survival gain (OSg) data were evaluated. Costs were calculated for 4-w, 12-month (m) in 1st line, 6-m for 2nd and 3-m for later lines. Intravenous drugs (iv) were computed for 70 kg or 1.7/m² sized patients. Cet (19, 20, 21) was given at a loading dose of 400mg/m² followed by 250mg/m² q week (w). Bev (22-24) was administered q 2w at 5.0mg/Kg in 1st- and 10mg/Kg in 2nd-line. Pan (25-27) was administered at 6.0mg/Kg, Afl 4.0mg/Kg (28) and ramucirumab (Ram) 8.0mg/Kg q 2 w. Reg (31-34) costs were calculated as 120 mg po daily dose for 3w q 4w. The 4wC of TAS 102 were calculated for 80 mg po bid on days 1 through 5 and 8 through 12 q 4w. Costs of FOLOX, FOLFIRI, IFL, downstream and treatment of adverse events (AEs) were not included. Dosage and frequency of drug administration were adhered to the published data and drug inserts as much as possible. The 4wC were rated A up to \$5,000, B >\$5,000 to 7,500, C: >7,500 to 10,000, D: > \$10,000 and avoidable if alternative drugs, clinical trials and cost concessions were available and possible. Costs/LYG (values) were graded A up to

100,000, B >100,000 to 200,000, C >200,000 to 300,000 and D >300,000. Values were expressed in relative values to 100,000 for drugs reported to maintain or improve QoL and 50,000 for lack of insufficient or inclusive data.

Results

A preliminary analysis of the 7 evaluated drugs in various multiple settings demonstrated median HR of 0.78, OS gain over control (OSg) 69 days and 4wC \$9,508. In 1st-line the 4wC and rating of Bev at 5.0mg/Kg were \$4,620 A. In KRAS wild type Pan demonstrated \$8,233 C and Cet \$9,775 C. Values (C/LYG) were shown in Table 1 with Bev rated A compared with Pan and Cet of C rating. The corresponding RV were 0.71, 0.49 and 0.28. For insured patients, a 20% out of pocket monthly co-payment of Bev, Pan, and Cet were \$924, \$1,647 and \$1,955 respectively. Bev maintained its economic advantage over Pan and Cet for 4 months.

Table 2 showed results of continuation of Bev at 5.0mg/Kg through and 2nd-line therapy and Bev used in 10mg/Kg (18,19). The monthly cost of Afl, a recombinant fusion protein which targets the vascular VEGF (20) was lowered by the parent company to \$5,000 resulting in favorable

cost and value ratings. Costs of Ram, an inhibitor of VEGFR2 (21) were \$11,200 with cost and value rating of D. The out of pocket monthly co-payments were: Bev \$ \$924-\$1,848 depending on the dose, Afl \$1,000 and Ram \$2,240.

Regorafenib and TAS 102 beyond the 2nd-line Table 3)

Reg, a small molecule multi-kinase inhibitor was reported to prolong OS in 3rd-line and refractory disease by 42 days at HR of 0.77(CORRECT) (22, 23). The 4wC was \$12,500 with D rating. With only 60% of patients receiving salvage therapy (24), the HR improved to 0.55 raising the value from D to C.

Trifluridine/tipiracil (TAS 102) (25) has recently been approved in refractory mCRC by the Federal Drug Administration (FDA) in US. The cytotoxic component Trifluridine is directly incorporated into DNA leading to its dysfunction. Tipiracil prevents the degradation and prolongs the half-life of Trifluridine. The 4wC were \$12,892 with a value of 257,800 and C rating. A 20% monthly co-payment was estimated at \$2,578, essentially similar to Reg of \$2,500. In view of inconclusive and/or insufficient data on QoL, the RV of Reg and TAS 102 could not be ascertained.

Discussion

Previous attempts to bend the cost curve of anticancer drugs (26-28) had met with limited success. In the present investigation, a simplified methodology was proposed to control and grade drug costs. We postulated that the society in the US would afford up to \$5,000 and avoid if possible 4wC > \$10,000.

Cost methodology based on cost/mg of drug or cost/OS gain over control in days (OSg) were too simplistic for medical economists and oncologists to use (29, 30). Cost/LYG and cost/QALY (31) are too elaborate for patients to understand how much they would be paying on a monthly basis for values in return. The 4wC could serve as a practical and expedient platform to bridge the communication gap between physicians and patients. Patients might drop out within 4-week treatments for lack of response or intolerance rendering costs of year-long assessment meaningless. There are multiple surrogates for endpoints (32). In the present study, only OS was used in drug evaluation and comparison. The simple intuitive design of the method would be helpful for the uninsured and low-to middle-income patients. Monthly payments and co-payments (33) could be rapidly disclosed in

advance by health professionals upfront prior to treatment.

Limitations

Costs of downstream and drugs other than those evaluated were not included. More importantly, the methodology failed to account for AEs and its treatment (34). Values were rated A for 100,000 to D 300,000 and expressed relative to 100,000 for drugs reported to maintain or improve QoL. The proposed values were approximate estimations rather than actual and real measurements of QALY and would fall within the acceptable cost-effectiveness ratios of \$50,000 - \$150,000 per quality QALY but higher than NICE costeffectiveness ratios (ACER) of 20,000-30,000. The value of QoL is difficult to quantify since it varies from patient and physician to another. The main limitation however was failure to cost accounting of Bev costs till-progression.

Application in mCRC

The costs and values of the monoclonal antibodies (MABs) in mCRC have been previously evaluated (35-36). However, there was scarcity of head to head drug comparison. Special attention was made in comparing one monoclonal antibody (MAB) or tyrosine-kinase inhibitor (TKI) with

another. Populations, controls, line of therapy, drug doses and frequency of administration varied between studies. It was interesting to observe that Bev 4wC at 5.0 mg/Kg in 1st-line were significantly lower than the proposed \$5,000 limits. Costs were markedly lower with higher values than Pan and Cet in wild RAS types. The wide separation of results would give credence to the conclusions that Bev values in 1st-line were worth paying for more than Pan and Cet. Of note, Bev demonstrated clinical activity in mCRC irrespective of KRAS mutation (37). Doubts on OS gain by Bev were raised (17). In the UK, Bev was not approved in 1st-line therapy.

In 2nd-line, costs of Bev at 10 mg/Kg was increased by twofold. Costs of Ram at \$11,200 were relatively high in agreement with previous report (38). Bev and Ram costs were markedly higher than the monthly Afl costs of \$5,000. The economic advantage of Afl over Bev and Ram was secondary to its relatively low costs rather than to its 48 OSg and 0.82 HR. Our preliminary data on Pan, Afl and Ram collectively suggested that costs were the primary driver in economic evaluation while values seemed to play secondary and dependent roles. These findings were in

agreement with the conclusions recently published by ASCO (7).

Regorafenib (Reg) and TAS 102

The 4wC of \$12,500 was far above the \$10,000 proposed limit raising concerns on its worth in refractory disease. The drug provided minimal incremental benefit at high cost/QALY (38). Reg cost of one added day of OS was too high for a modest 42-day gain (27). The AEs were reported to be serious and problematic (22-23). The results of the CONCUR study (24) suggested better outcome in less heavily treated patients. At HR of 0.77 in the CORRECT study, values were significantly better than at HR of 0.55 in the CONCUR study. The newly approved TAS 102 demonstrated an OSg of 54 days with HR of 0.68 at \$12,890 costs. The safety profile was reported to be acceptable (25).

The convenient oral administration of Reg and TAS 102 should result in cost savings over the iv administration of chemotherapeutic drugs as reported with capecitabine (39). Nonetheless, considering the clinically modest OSg of < 60 days the costs could be considered excessive for their values particularly if used at the end of life scenarios.

Future trends in cost analysis

Generics and biosimilars (40) have been successful tools to control costs, the importance of biomarkers has been highlighted in mCRC. A small subset of patients usually responds to the anti-angiogenesis inhibitors (41). Finding a biomarker of response would spare non-responders the burden of drug costs and render drugs worth paying for (42). At present, it is imperative to maintain a fair balance between patients' benefits and the high costs of innovations (43) and litigations incurred by pharmaceutical companies.

Conclusions

Methodology to grade costs and values of anticancer drugs could serve as a practical approach to control costs and facilitate communication with patients. Application in mCRC was feasible, fast and user-friendly. The 4wC of Bev in 1st-line were affordable and significantly lower with higher values than Pan and Cet. Costs of Ram, Reg and TAS 102 were considered excessive > \$10,000.

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Table 1**Costs and Values of MAB in 1st line mCRC**

Drug/combination	OS gain (days) (OSg) & HR	4wC (US\$) Grade	C/LYG	RV⁺:100,000 per C/LYG
FOLFOX ± Pan 6.0mg/Kg q 2 w x 2 cy, wild KRAS (10,11)	132 & 0.83 CI 0.70, 0.98	8,233 C	269,444 C	0.37
FOLFOX ± Pan q 2 w x 2 cy, extended RAS (12)	174 & 0.78 CI 0.62 - 0.99 P= .04	8,233 C	204,406 C	0.49
Cet q w x 4 w (4 cycles) wild KRAS (retrospective) (13)	141 & 0.55 CI 0.41 - 0.74 P <0.0001	9,775 C	299,289 C	0.33
FOLFIRI ± Cet q w x 4 w, wild KRAS (14, 15)	120 & 0.80 P =.0093	9,775 C	351,900 D	0.28
IFL± Bev q 2 w, 5.0mg/Kg x 2 cy (16-17)	141 & 0.66 P <0.001	4,620 A	141,549 B	0.71

Table 2**Costs and Values of MAB in 2nd- line**

Drug/combination	OSg & HR	4wC Grade	C/LYG Grade	RV*: 100,000/ C/LYG
Chemo ± Bev continued through 2 nd -line (TML)(18)	42 & 0.83 CI 0.71- 0.97 P = .021	4,620 A	158,400 B	0.63
FOLFOX ± Bev 10mg/Kg q 2 w x 2 cycles, Bev-naïve (E- 3200)(19)	63 & 0.75 P = .0051	9,240 C	316,800 D	0.32
FOLFIRI ± Afl 4.0mg/Kg q 2 w x 2 cy (Velour)(20)	48 & 0.82 CI 0.71 - 0.94 P = .0032	5,000 A	225,000 C	0.44
FOLFIRI ± Ramucirumab (Ram) 8.0mg/KG q 2 w x 2 cy (RAISE)(21)	48 & 0.84 CI 0.73 – 0.98 P = .0219	11,200 D	504,000 D	0.20

Table 3**Regorafenib and TAS 102 in refractory mCRC***

Drug	OSg & HR	4wC Grade	C/LYG Grade
Reg 160mg po daily for 3 w q 4 w (one cycle) 3 rd and refractory (CORRECT) (22,23)	42 & 0.77 CI 0.64 - 0.94 P = .0052	12,500 D	321,429 D
Reg, Asian patients with 60%pretreated (CONCUR) (24)	75 & 0.55 CI 0.40 - 0.77 P = .00016	12,500 D	180,000 B
Trifluridine/tipiracil (TAS 102) (RECOURSE) (25)	54 & 0.68 CI 0.58 - 0.81 P< .001)	12,890 D	257,800 C

*The RV could not be estimated in view of unavailable or inconclusive data on QoL.