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The right amount of chemotherapy in non-curable disease: Insights from health economics



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ABSTRACT

This article applies concepts from health economics to address what is the “right” amount of chemotherapy in non-curable disease. A health economics perspective is beneficial because it forces a focus on objectives and constraints. We review and apply the concepts of “Choice of Comparator”, “Use of QALYs” and “Equating Marginal Benefit to Marginal Cost”, demonstrating their fit for purpose when considering the optimal amount of chemotherapy for non-curable disease. Many efforts underway to improve healthcare can be viewed as applications of these key economic principles. The true value is in the concepts themselves and not in the associated calculations. Given the difference between a population and a patient perspective, different “optimal” amounts of chemotherapy may exist. For many, however, best may not be most. Optimal decisions may vary depending on whether the goal of treatment is to maximize hope or health.

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1. Introduction

In a recent *Forbes* post entitled, “The FDA Is Basically Approving Everything”, Matthew Herper argues that the Food and Drug Administration’s approval rate for new drugs is over 95% [1] in sharp contrast to when it “once approved as few as 40% of new drugs” [2]. This trend produces pressure around the world for healthcare providers to prescribe and healthcare payers to fund these new products. There is agreement throughout medicine and especially in oncology that the current rate of growth in healthcare expenditures is unsustainable [3,4]. Recently published warnings have appeared in both general and specialty medical journals [5,6]. Experts note that the direct medical costs of cancer in the USA have increased from nearly \$27 billion in 1990 [7] to more than \$90 billion in 2008 [8] more than two-fold increase even after adjusting for inflation [9]. Smith and Hillner [4] report that annual direct costs in the USA for cancer care are projected to increase by over 66% from \$104 billion in 2006 to over \$173 billion in 2020 [4,10].

In cancer, there has been a pronounced focus on the cost of drugs in relation to their clinical benefits. Bach [11] observed that spending from 1997 to 2004 on Medicare’s Part B drugs, “a category dominated by drugs used to treat cancer”, increased by 267% compared with overall Medicare spending which increased by 47% during the same period. The problem of skyrocketing drug costs is compounded by evidence suggesting that increased expenditures are producing only minimal gains in terms of decreases in mortality and increases in quality of life [11]. In other words, healthcare payers are paying more and getting less [12]. In her editorial, “Why do drug companies charge so much? Because they can”, Marcia Angell observes that “Unlike every other advanced country, the United States permits drug companies to charge patients whatever they choose” [13].

Although the USA has taken steps to prevent the simultaneous examination of both drug costs and patient outcomes [11,14], other countries have embraced methods from health economics to address the challenge of introducing controls in an attempt to curb healthcare spending [15–17]. First and foremost, cost-effectiveness analysis (CEA) has been implemented in a variety of settings to help with “smart shopping” for cancer drugs. However, there are other health economics concepts that can help, especially with address-

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ing the question of chemotherapy. This paper describes and then applies three principles from health economics to consider the “right” amount of chemotherapy for non-curable disease.

2. Principles

In this section we describe the economic principles we will demonstrate later in the Application section. The three key principles are

- 1) To compare treatment options, a comparator is needed;
- 2) Quality Adjusted Life Years (QALYs) are useful when considering both quality and length of life;
- 3) Optimal care occurs when the marginal benefit equals the marginal cost of care.

We now describe and explain each principle in more detail.

2.1. To compare treatment options, a comparator is needed

An essential part of any evaluation is the choice of a comparator. In economic evaluations of healthcare interventions and treatments, “something new” is often compared to “usual care”. In CEA, the extra costs (ΔC) are compared to the extra effects (ΔE) with ΔC computed as the difference between the expected costs of the new treatment (C_{NT}) and the expected costs of usual care (C_{UC}); ΔE is computed in a similar fashion using a patient outcome chosen to be the *Effect* variable. The term “expected” is used in the statistical sense, where outcomes are weighted by their respective probabilities of occurrence. For example, with a new drug there might be a 50% chance of living 9 more months and a 50% chance of living 1 more month. The expected effect of the new treatment (E_{NT}) is

$$E_{NT} = \frac{1}{2}(9\text{months}) + \frac{1}{2}(1\text{month}) = 5\text{ months.}$$

If patients receiving usual care are expected to live 4 months, then $\Delta E = E_{NT} - E_{UC} = 5 - 4 = 1$ more month.

Simply knowing the new treatment’s expected effect (E_{NT})—or expected cost (C_{NT})—is not enough to do comparative analysis, such as economic evaluation. This is because the calculation of ΔE involves two components (i.e., E_{NT} and E_{UC}) as does the calculation of ΔC . In addition, the choice of a different comparator frequently yields different estimates of ΔC and ΔE . For example, if usual care instead were associated with an expected patient outcome of 7 months of life, then $\Delta E = E_{NT} - E_{UC} = 5 - 7 = -2$ (i.e. 2 less months). Thus, CEA relies on four expected values for the estimation of ΔC and ΔE to inform policy and practice decisions. This is impossible to do without a choice of comparator.

An appropriate comparator has a large impact on the finding of effectiveness and ‘value for money’ of a treatment. Traditionally, palliative care interventions as ‘usual care’ have not been compared against chemotherapy for best care in end of life. However, where they have, there is evidence for the potential of improved quality of life (and sometimes even improved life expectancy [18]).

2.2. Quality adjusted life years (QALYs) consider both quality and length of life

Health economists often study the efficiency of different ways to accomplish an objective. When considering toxic treatments for incurable disease, a reasonable objective could be to maximize an outcome with quality of life (*qol*) and length of life (*lol*) dimensions. In these circumstances, health economists use the quality adjusted life year (QALY) which is equal to the product of *qol* and *lol*. The *qol* variable is called a “utility weight” and generally ranges between

0 (death) and 1 (perfect health) [19]. When QALYs are taken as the outcome of interest, the resulting economic evaluation is often described as a cost-utility analysis [20].

In these cases, the extra effects are calculated as extra QALYs ($\Delta QALYs$). For example, a complete course of highly toxic chemotherapy may allow patients to live 6 months on average with a quality of life utility score of 0.60. Perhaps with good palliative management patients can be expected to live 4.5 months with a quality of life utility score of 0.80. The additional QALYs from the new chemo are calculated as

$$\Delta QALYs = QALYs_{\text{newchemo}} - QALYs_{\text{palliativecare}}$$

$$\begin{aligned} \text{The } QALYs_{\text{newchemo}} &= qol_{\text{newchemo}} \times lol_{\text{newchemo}} \\ &= 0.60(\frac{1}{2}\text{year}) = 0.30QALYs. \end{aligned}$$

This is the same as the result from the calculation of

$$\begin{aligned} QALYs_{\text{palliativecare}} &= qol_{\text{palliativecare}} \times lol_{\text{palliativecare}} \\ &= 0.80(0.375\text{ year}) = 0.30QALYs. \end{aligned}$$

Thus, $\Delta QALYs = 0$. QALYs are a relevant way to consider different amounts of chemotherapy, especially with non-curable disease. However, some critics argue that the QALY may not capture adequately quality of life at the end of life, which is relevant for the majority of high-cost cancer drugs that provide limited gains in life extension in the last year of life [21]. To reach a decision about the optimal amount of chemo, marginal benefits and marginal costs must be considered.

2.3. Optimal is where marginal benefit equals marginal cost

To maximize Net Benefit (NB), which is the difference between Total Benefits (TB) and Total Costs (TC), it is necessary to consider marginal benefit (MB) and marginal cost (MC). The term “marginal” describes the resulting “extra” for very small changes in consumption or use. Technically, $NB = TB - TC$ and the quantity that maximizes NB is one such that $MB = MC$. Intuitively, if more chemo would add benefit greater than its additional costs (i.e., $MB > MC$) then one should consume more chemo. Alternatively, if the additional cost of more chemo is greater than the additional benefit (i.e., $MB < MC$), it does not make sense to consume more (it makes sense to consume less). An optimal amount occurs when $MB = MC$, as the gain in benefit from doing a bit more or a bit less equals the increase in costs (so the gain in NB is zero). Although traditionally benefits and costs are thought of in monetary units, it is only necessary that they be in the *same* units. For example, benefits and costs could be considered in terms of usefulness, satisfaction, energy or effort. Regardless of the units employed, the optimal quantity of chemo is the level at which $MB = MC$. This simple rule can lead to counter-intuitive recommendations when applied; for example, the best amount of treatment may not be most amount of treatment.

3. Application

Next, we apply the principles described in the previous section to analyze what is the right amount of chemotherapy in non-curable disease. We assume a patient can receive an amount of chemo (*chemo*) for a non-curable disease ranging from 0% and 100% of the patient’s remaining time. The optimal level of *chemo* can differ by perspective. While applying the economic principles, we illustrate contrasts between a population and an individual perspective.

3.1. The choice of comparator and the creation of expectations

We begin by considering patients whose usual care involves full chemo for their non-curable disease (i.e., *chemo* = 100%). There are other treatments that could be considered for non-curable disease. We label such a treatment alternative “new treatment” (i.e., *chemo* < 100%). As noted above, economic analysis considers ΔE based on new treatment vs. usual care. Table 1 presents hypothetical evidence with which ΔE can be computed.

Based on the first row of Table 1, with usual care, there is a 50% chance of living 9 months and a 50% chance of living 1 month, so the expected outcome is 5 months (as computed in the previous section). Alternatively, patients receiving new treatment have an expected outcome that can be computed as $\frac{3}{4}$ (4 months) + $\frac{1}{4}$ (2 months) = 3.5 months, so $\Delta E = E_{NT} - E_{UC} = 3.5 - 5 = 1.5$ less months.

Expected outcome (and therefore ΔE) is a population concept not an individual concept. The difference in population vs. individual perspective can be understood in the interpretation of the last column. The “expected outcome” of 5 months does not mean patients can expect to live 5 months; in fact, 0% of patients receiving usual care will live 5 months, even though the expected outcome is 5 months. The expected outcome is useful when considering a population of patients. Of 1000 patients treated with usual care, 500 will live 9 months and 500 will live 1 month for a total gain of $4500 + 500 = 5000$ months. In contrast, we expect that 1000 patients treated with new treatment will yield 750 patients living 4 months and 250 patients living 2 months for a total gain of $3000 + 500 = 3500$ months. From a population perspective new treatment provides $3500 - 5000 = 1500$ less months for a population of 1000 patients or $1500/1000 = 1.5$ less months per patient. Thus, the expected value is a useful concept for considering the effect of policy decisions on a population of patients. However, it is possible that not a single patient will experience the “expected” effect of treatment.

Patient-based decisions may involve other considerations besides maximizing expected outcome. For example, what if a patient wants to be present at an important event 6 weeks in the future? In this case, the new treatment is optimal, since there is a 50% chance this will not happen with the choice of usual care. With usual care, for every patient who lives 9 months there is a patient who dies at 1 month (before the important event 1.5 months away). With new treatment, all patients survive at least 2 months. Looking at the “bad case” scenario in Table 1, from a population perspective, the two treatment options have the same expected value; however, from a patient perspective being twice as likely (50% vs. 25%) to live half as long (1 month vs. 2 months) may not be perceived as equivalent. And for some wanting to minimize the possible loss in a worst case scenario, the new treatment is actually better than usual care (2 months vs. 1 month). Research on end of life care is rich in examples of where the maximization of expected health may not be the only objective (e.g., the application of prospect theory [22,23] and the implications of valuing hope [24–26], etc.). For many patients, quality of life is an important consideration.

3.2. Quality adjusting life years (QALYs)

When applying the concept of QALYs to the choice of how much chemotherapy for non-curable disease, we assume that length of life (*lol*) increases at the expense of decreased quality of life (*qol*). This trade-off can be visualized with treatment options A through E on the downward sloping solid line in Fig. 1.

In this example, the goal of maximizing QALYs occurs with the optimal treatment option labeled “Opt”, as can be seen on the dashed curve in Fig. 1. For patients currently receiving treatment option B, a longer life with lower quality of life yields more QALYs;

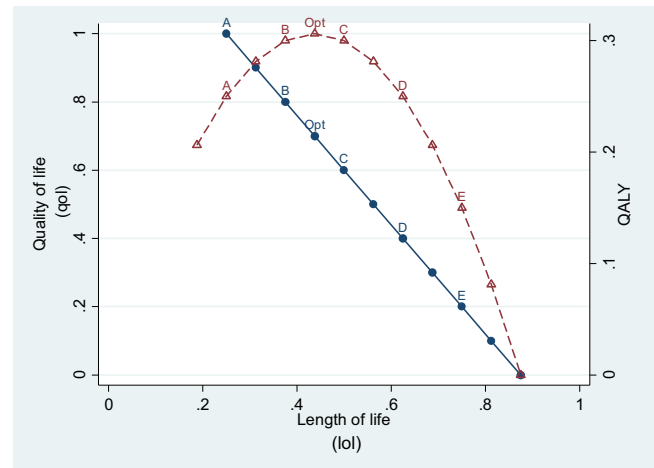


Fig. 1. The trade-off of longer life with lesser quality of life.

however, for patients receiving treatment option C, a shorter life with more quality of life yields more QALYs.

The dashed upside down curve in Fig. 1 shows the QALYs from each treatment option (Options B and C are at the same height of 0.30 since they yield the same number of QALYs). The maximum QALYs a patient can experience occurs where the slope of the QALYs curve is zero. At this point, with a little more *lol* or a little less *lol*, no additional QALYs are gained. The optimal condition can also be written as

$$\epsilon = -1$$

where ϵ is the ratio of the percentage change in *qol* divided by the percentage change in *lol*.¹ When considering the treatment options in Section 2.2, if we assume that they represent options along a line (like that in Fig. 1), we can calculate the slope as

$$\Delta qol / \Delta lol = (0.60 - 0.80) / (0.500 - 0.375) = -0.2 / 0.125 = -1.6.$$

The ϵ value at the point² for new chemo where *lol* = 0.5 years and *qol* = 0.60 is $-1.6 \times 0.5 / 0.6 = -1.33$. The ϵ value at the point for palliative care where *lol* = 0.375 years and *qol* = 0.80 is $-1.6 \times 0.375 / 0.8 = -0.75$. Since neither $\epsilon_{\text{newchemo}}$ nor $\epsilon_{\text{palliativecare}} = -1$, this means both palliative care and new chemo treatment options can be improved upon; however, the direction for improvement differs. Since $\epsilon_{\text{newchemo}} = -1.33 < -1$, this means there will be a 1.33% loss in *qol* with a 1% gain in *lol*. This indicates reducing *lol* to gain *qol* is optimal. In contrast, since $\epsilon_{\text{palliativecare}} = -0.75 > -1$, there will be a 0.75% loss in *qol* from a 1% gain in *lol*. This indicates increasing *lol* while losing *qol* is optimal because there is an overall gain in QALYs. In general, a simple rule to determine the overall percentage change in QALYs from a percentage change in *lol* is $\epsilon_{\text{QALY}, lol} = (1 + \epsilon_{qol, lol})$.³ Thus, when $\epsilon_{qol, lol}$ for new chemo = -1.33 , increasing *lol* will lead to an overall decrease in QALYs (since the decrease in *qol* will be proportionally greater than the increase in *lol*). In contrast, when $\epsilon_{qol, lol}$ for palliative care = -0.75 , increasing *lol* will lead to an overall increase

¹ As $\text{QALYs} = qol \times lol$, and we have assumed *qol* is a function of *lol*, this means the optimal *lol* sets $\Delta \text{QALYs} / \Delta lol = (\Delta qol / \Delta lol \times lol + qol) = 0$. Dividing both sides by *qol*, the optimal *lol* satisfies the equation $(\Delta qol / \Delta lol \times lol / qol + 1) = 0$. This can then be simplified to $(\% \Delta qol) / (\% \Delta lol) = -1$ where $\% \Delta qol = \Delta qol / qol$ and $\% \Delta lol = \Delta lol / lol$.

² The expression for ϵ can be written in terms of a slope and a point. For example, since $\epsilon = (\Delta qol / qol) / (\Delta lol / lol)$ this means $\epsilon = (\Delta qol / \Delta lol) \times lol / qol$, so $\epsilon = \text{slope} \times lol / qol$.

³ For small changes, $\Delta \text{QALY} = \Delta qol \times lol + \Delta lol \times qol$, so $(\Delta \text{QALY}) / (lol \times qol) = (\Delta qol \times lol + \Delta lol \times qol) / (lol \times qol)$. Simplifying, $\% \Delta \text{QALY} = \% \Delta qol + \% \Delta lol$. After factoring out, $(\% \Delta \text{QALY}) / (\% \Delta lol) = 1 + (\% \Delta qol / \% \Delta lol)$.

Table 1
Hypothetical evidence on hypothetical treatment options.

	Outcome in good case (probability)	Outcome in bad case (probability)	Expected outcome
Usual Care of chemo = 100%	9 months (50%)	1 month (50%)	$E_{UC} = 5$ months
New Treatment of chemo < 100%	4 months (75%)	2 month (25%)	$E_{NT} = 3.5$ months
Difference	1.5 months	0	$\Delta E = -1.5$ months

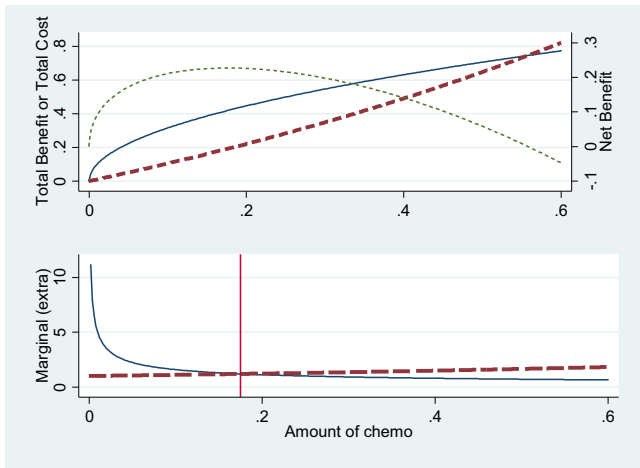


Fig. 2. Optimal choices occur where Marginal Benefit equals Marginal Cost.

in QALYs (since the decrease in *qol* will be proportionally less than the increase in *lol*). Only when $\varepsilon_{qol,lol} = -1$, does $\varepsilon_{QALY,lol} = 0$, resulting in $\Delta QALY = 0$.⁴

While the mathematical process to calculate QALYs does not differ at the population and patient levels, the actual value of the QALY (and treatment implications) may. For one type of patient, chemo may be consistent with treatment options like A or B in Fig. 1. However, for another type of patient, chemo may be consistent with treatment options like C, D or E in Fig. 1. If treatment response is heterogeneous, ε may differ by patient, and so too will the attractiveness of additional chemo. Likewise, a patient may ascribe a *qol* weight that is different from the population average. Even different countries have different utility weights for the same health state. For example, nearly 90% of all *qol* weights for the UK vs. the US vary by ≥ 0.10 (based on author calculations using the EQ-5D-5L) [27]. Needless to say, decisions to maximize QALYs at a population level may not be congruent with decisions to maximize an individual’s QALYs, even if ε is used for guidance. For example, prospect theory assumes that patients value outcomes not in absolute terms, but as deviations from their point of reference; different people may have different reference points (leading to different optimal levels of chemo) [22,23].

3.3. Marginal benefit (MB) equals marginal cost (MC)

Additional benefits usually come at an additional cost. When considering additional chemo for non-curable disease, one must ask, “When is enough enough?” The answer from economics is that the best amount of chemo is the amount that maximizes Net Benefit; this amount of chemo equates Marginal Benefit with Marginal Cost (i.e., $MB = MC$). Marginal is the slope of the Total or the result of doing a bit more (or less). It can be calculated as the first derivative of the Total. Fig. 2 illustrates these points with two graphs. The upper graph in Fig. 2 shows Net Benefit (as a dotted upside down

curve), Total Benefit (as a solid line) and Total Cost (as a heavy dashed line).

The slopes of the Total Benefit and the Total Cost curves are the Marginal Benefit and the Marginal Cost curves, respectively. The Marginal curves are plotted in the lower graph in Fig. 2, MB as a solid curve and MC as a heavy dashed line. The vertical line at $chemo = 0.175$ indicates the optimal amount of chemo where $MB = MC$. While this point is neither where Total Costs are minimized nor where Total Benefits are maximized, it is where the patient receives the most NB. Thus, economic analysis is able to distinguish between the most amount of chemo, the least amount of chemo and the best amount of chemo by considering the MB and MC of chemo for non-curable disease.

The mathematical process to calculate MB and MC does not differ at the population and patient levels; however, the actual value of the marginal values may vary to the extent that the formulations of Total Benefit and Total Cost vary between a population and a patient. Also, as noted earlier, benefits and costs are usually considered in monetary units, but they also can be thought of in terms of usefulness, satisfaction, energy or effort. A healthcare payer taking a population perspective might consider the MB and MC of chemo for non-curable disease much differently from a patient. Regardless of the units employed, the optimal quantity of chemo is the level at which $MB = MC$. Likewise, if treatment response is heterogeneous, MB and MC may differ by patient, and so too will the attractiveness of additional chemo. Of course, it is also possible for MB and MC to differ by country [23].

4. Discussion

4.1. Implications

When considering the “right” amount of chemo for non-curable disease, health economics principles can be useful. The three main concepts that we reviewed and applied involved the importance of (1) a comparator; (2) using QALYs and (3) treating until $MB = MC$. The applications of these principles produced insights like

- 1) 100% chemo is one choice that must be compared to another option having its own expected costs and effectiveness, since there is never just one option from an economic perspective;
- 2) Increasing length of life is not always synonymous with increasing quality-adjusted life; and
- 3) The best amount of treatment can be neither the most nor the least amount of treatment.

The implications for choice of care (e.g., palliative care vs. chemo care) are clear. Considering only one option for care for non-curable disease is not a helpful way to facilitate an informed choice. Considering only one dimension of outcome (e.g., length of life only) is not helpful if quality adjusted life years is what patients want from their treatment of non-curable disease. Lastly, considering only Total Benefit and Cost is not optimal when selecting the right amount of chemo. What matters is the *extra* benefit and *extra* cost (i.e., MB and MC) that are derived from considering decreases (or increases) in chemo for non-curable disease. When patients are being treated with the “right” amount of chemo then a little more (or a little less) helps the patient as much as it hurts the patient; this is where we

⁴ If $\varepsilon_{QALY,lol} = 0$, this means $\% \Delta QALY / \% \Delta lol = 0$, so $\% \Delta QALY = 0$; therefore, $\Delta QALY = 0$.

should stop from a patient's perspective. If patients value hope, healthcare payers may be pressured to pay for expensive chemo regimens to provide it [28]. Intrinsically, there is nothing wrong with paying for hope; however, efficient use of scarce resources would dictate that one should look for efficient and cost-effective ways to give real hope to individuals. Also, from a population or a provider's perspective, there may be different answers to questions about correct comparator to use, QALYs gained, or amount of chemo to equate MB and MC.

4.2. Strengths and limitations

There are limitations associated with our work. Obviously, there are other relevant concepts from health economics that were not directly discussed (e.g., opportunity cost [29–31], incentives [32–37]). More fulsome discussions of how to apply economic thinking to healthcare appear elsewhere [38,39]. In addition, some readers may be critical of the need for calculation to determine optimality, arguing that assumptions limit the practical use of these concepts. To illustrate some of the concepts, we did make simplifying assumptions (e.g., the linear, negative trade-off between quality of life and length of life). However, many of the concepts apply with less simplistic specifications or in circumstances where additional chemo is associated with *both* additional gains in length of life and quality of life. Also, we may never know the exact specification of the specific functional form for Total Benefit and Total Cost equations. However, one may not need calculus to prove that dying in the emergency room from a chemo related adverse event during the last stage of metastatic disease may not be optimal; clearly the marginal benefit of treatment is not worth the marginal cost. It is the concepts, not the calculations that are of value. The next challenge in cancer care for non-curable disease will be to apply them.

5. Conclusion

The economic perspective on cancer care when a cure is not possible is beneficial because it forces a focus on objectives and constraints. We reviewed and applied the concepts of “Choice of Comparator”, “Use of QALYs” and “Equating MB to MC”, demonstrating how they fit when considering the question of the optimal amount of chemo for non-curable disease. Many current efforts underway to improve healthcare can be viewed as applications of these key economic principles e.g., the ABIM Foundation's Choosing Wisely [40], the Institute for Healthcare Improvement's Triple Aim [41], the pan-Canadian Oncology Drug Review's Deliberative Framework [42], or the Cancer Drug Fund in the UK [43,44]. While it may be difficult to quantify when applying some of the concepts, the true value is in the concepts themselves (not in the calculation). However, it is important to remember that perspectives differ, so different “optimal” amounts of chemo may exist and these may vary by perspective. Healthcare is tricky because our aim may be to make everyone live longer and better, but we cannot afford that for everyone; we must find a way, within publicly funded health systems to define how much society and individuals are willing to sacrifice to live longer and better. And, in some cases, living better may include using scarce healthcare resources to foster a stronger sense of hope. Health economics provides some structures to debate healthcare spending; they are imperfect, but defining best care for patients and a population is never easy.

To many, it is clear that cancer drug costs are of concern [6,45–48]. However, even for patients with non-curable disease who are fully insured or independently wealthy, there is a scarce resource and that is quality time. For them, even with chemo that has zero financial toxicity, best may not be most [49].

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