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Reviews

Value and cancer medicines—A personal view

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ABSTRACT

This paper outline the attributes of new medicines that are perceived to offer added clinical value by those making decisions about pricing and reimbursement, often called 'payers'. It also describes other attributes that, although they may represent some progress in cancer care, may not represent added value for which a payer would wish to pay, and some more controversial areas where there is some debate and difference of view on whether added value exists. A review of data from the Scottish Medicines Consortium (SMC) shows that median lifetime QALY gain for all new medicines assessed was 0.14 QALYs (mean 0.59 QALYs). Oncology medicines showed slightly greater median QALY gains, with 0.37 QALYs for medicines for early or adjuvant therapy (n = 49) and 0.26 QALYs for medicines for advanced cancer (n = 38); mean health gain was 0.51 QALYs for both groups.

The discussion of value assessment is structured in three parts; accepted elements of clinical value, questionable clinical value and doubtful clinical value. A review of non-acceptance decisions reveal that cost-effectiveness considerations sometimes played a role for the decision, but it is clear that other factors, such as limited information on clinical benefit, concerns about extrapolation from trial data and failure to take account of prevailing clinical practice, were part of the failure to demonstrate the value of these medicines.

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1. Introduction

The last two decades have seen very welcome progress in the treatment of most cancers, with an expanding range of increasingly effective medicines targeted on the disease at most of its stages. These new treatment options have, however, faced healthcare systems with significant increases in cost per patient treated, posing an increasing financial burden on the limited resources available.

Many healthcare systems (and in systems with significant patient co-payments, many patients) have sought to assess the real clinical value of new medicines to allow decisions about provision or reimbursement to be made on the basis of clinical evidence. As most cancers now have at least some treatment options, it is generally the incremental clinical benefit (over existing therapy) that represents relevant clinical value. While some clinical experts have defined value in a rather narrow context, looking only at survival (overall survival and/or progression-free survival) with or without quality of life benefits, this approach may fail to capture all relevant factors for assessing the value of new medicines from a payer perspective.

This paper, therefore, aims to outline the attributes of new medicines which are perceived to offer added clinical value by those tasked with decision-making in this context (often called 'payers' as they are thought to be taking the perspective of the real payers in a healthcare system). It also describes other attributes that, although

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they may represent some progress in cancer care, may not represent added value for which a payer would wish to pay, and some more controversial areas where there is some debate and difference of view on whether added value exists.

Different countries have very different ways of relating added clinical value to financial cost or reimbursement. Some, such as the United Kingdom and Sweden, use formal cost-effectiveness assessment, while others use different methods to relate added clinical value to price and 'willingness to pay'. Consideration of these different systems is beyond the scope of this paper, but in each system it is added clinical value that is sought to justify any increased cost, and it appears that the components of that added value are essentially similar in most systems.

The author has over 20 years experience in assessing the clinical value and cost-effectiveness of new medicines, including cancer medicines, culminating in chairing the Scottish Medicines Consortium (SMC – 2008–2011). This role has brought him into contact with many payers from other healthcare systems and led to frequent discussions around the concepts and components of added value. These informal discussions are rarely the subject of published scientific papers, so this paper is a personal view based on these informal interactions rather than an evidence-based review.

2. Value of cancer medicines – does it matter?

There is sometimes an assumption that new medicines for cancer treatment are usually major advances in therapy, and thus that their added clinical value can be taken for granted. In 2011, the Scottish Medicines Consortium (SMC), which reviews almost all new medicines coming to the UK marketplace, looked at the lifetime health gain claimed for almost 300 medicines by their manufacturers using the metric of the Quality Adjusted Life Year (QALY). The QALY is an internationally used tool to combine improvements in survival and changes in Health Related Quality of Life (HRQoL) in a single metric, and has the advantage of not being specific to any single disease area, allowing comparisons of clinical value across different clinical contexts. One QALY is equal to one year of life at 100% quality of life – 0.5 QALY could be 6 months at 100% quality of life or 1 year at 50% quality of life (for example).

Median lifetime QALY gain for **all** new medicines assessed was 0.14 QALYs (mean 0.59 QALYs). Oncology medicines showed slightly greater median QALY gains, with 0.37 QALYs for medicines for early or adjuvant therapy (n = 49) and 0.26 QALYs for medicines for advanced cancer (n = 38); mean health gain was 0.51 QALYs for both groups, very similar to non-cancer medicines. These figures showed that, while new oncology medicines did offer health benefits over existing therapies, the benefits were generally quite modest, which is important as many of the newer medicines come at considerably higher cost than existing treatments (Table 1).

In keeping with these data is the finding that very few cancer medicines achieve high classifications in terms of clinical benefit in either the German or French medicines assessment systems, neither of which uses the QALY as a measure of benefit but each of which tries to find added clinical benefit in their own way.

In countries that use a formal cost-effectiveness assessment process, it will usually be the mean health gain (=mean QALY gain) that is taken to represent the clinical value as this captures the overall health improvement (including the effects of 'outliers') better than the median. That the mean QALY gains are significantly higher than the median QALY gains reflects significant skewing of QALY benefits, with a small number of patients often experiencing greater benefits than the majority.

It is frequently argued that QALY gain, while important, may not capture all the value of a new medicine, so the rest of this paper looks at suggested components of value, some of which go beyond QALY gain, and their potential roles in providing added value.

3. Added clinical value

Overall survival – the principal adverse effect of a diagnosis of cancer is the possibility (and for some cancers, the probability) that life expectancy will be shortened. The extent of this effect varies substantially between individual cancers, with cure possible in some (e.g. leukaemias, testicular cancer), a more chronic course being run in others (e.g. breast and prostate cancer) and a much shorter and more acute course in others (e.g. lung and pancreatic cancer). The aim of most new medicines in cancer, whether used in a therapeutic or adjuvant/neo-adjuvant setting, is to improve overall survival and thus reduce the adverse impact of the cancer diagnosis on life expectancy.

Improvements in cancer survival are therefore viewed as added clinical benefit for which payers would generally wish to pay. Often the improvements in overall survival, even where reasonably certain, are modest in magnitude (e.g. small numbers of weeks), and a payer may be uncertain whether there is truly significant added value over existing treatment. This is especially true where the population studied in clinical trials is rather different from the patient population likely to be treated (in terms of age, performance status, co-morbidities etc), when the benefits apparently shown in the main clinical trials might not actually be achieved in real clinical practice.

While it is a 'hard' endpoint, overall survival is often uncertain from clinical trial data, either because the medicine reaches the marketplace before overall survival data are known or because the clinical trial protocol has allowed 'cross-over' from the 'usual treatment' arm to the new medicine arm at a point when benefit (e.g. on progression-free survival (PFS)) has been shown. While OS data may eventually become available in the former situation as data mature, it will never be known with certainty in the latter setting.

Given the importance of overall survival, methods have been developed to attempt to allow for the effects of cross-over. Rank-preserving structural failure time (RPSFT) modelling and other techniques offer ways to estimate OS using trial data. Simpler techniques, such as using historical control data, are less satisfactory as earlier diagnosis of many cancers is producing an element of 'lead-time bias', where the time from diagnosis to death is increasing over time, not due to more effective treatment but to earlier diagnosis. Assessing the impact of a new medicine against historical controls is thus very likely to over-estimate the true survival benefit of the medicine.

While all increased OS is valued by payers, most will view this as an added clinical benefit more enthusiastically when the extra survival occurs sooner rather than later – thus an extra 6 months survival will be more highly valued if it occurs 6 months from now rather than anticipated 5 years from now. In some systems this is formalised by discounting future benefits at a fixed rate, while the assessment is less formalised, though still present, in other systems.

Health-related Quality of life – following a diagnosis of cancer, patients fear, and clinicians seek to avoid, a progressive decline in HRQoL with increasingly severe symptoms (e.g. pain, dyspnoea) and decline in functional capacity and independence. Payers recognise this issue and are generally willing to pay to either improve HRQoL or delay/minimise decline in HRQoL. They will usually take a wide perspective, and regard benefits in HRQoL as desirable and valuable whether they relate to the effects of the cancer itself or the impact of cancer therapies (see Tolerability below).

In addition to valuing improvements in or maintenance of HRQoL, payers are also interested in the absolute HRQoL of patients, to ensure that improved survival outcomes are being achieved with