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Not cost-effective at zero price: valuing and paying for combination therapies in cancer

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Introduction

Combination therapies are used to treat many cancers. Recently it has become common for newly developed add-on treatments to be combined with existing treatments that are relatively new and on-patent. This can result in high costs, leading to affordability challenges

for payers and to therapies often being found to not represent value for money by health technology assessment (HTA) agencies and pricing and reimbursement bodies [1]. As a result, patient access to effective novel combination therapies for cancer may be restricted or denied in many health systems.

It is not unusual – or in itself a problem – for some treatments to be considered poor value for money. Limits on healthcare budgets mean opportunity cost lies at the heart of HTA. However, when patient access is at risk for a whole category of new, clinically effective treatments, this becomes an important issue. Cost-effectiveness challenges with new treatments can generally be addressed by negotiating treatment price. But some clinically effective combination therapies would not be cost-effective even if the price of the new treatment being added to an existing one was zero. This seems illogical and presents unique challenges to achieving patient access. In this editorial we summarise these problems and consider how they might be addressed.

Combination Therapy: Costs and Value

Challenges associated with the cost and valuation of combination therapies have been outlined before [1-5]. Consider two scenarios. First, a case where two existing monotherapies are combined. For simplicity, assume that no other active treatment exists, and, also, that the only costs are the price of the treatments. Imagine that both bring an incremental value over no active treatment of 'Δv' when given alone, and are priced to incremental value, so have the same price, say 'p'. Now imagine that combining the drugs provides an incremental value of 1.5Δv, at an incremental cost of 2p. The incremental cost of therapy has doubled, but incremental value has not. Hence, the combination would probably not be considered good value for money. If an active standard treatment exists and other treatment costs are included, the mathematics become more complicated, but the same argument holds and the incremental value of the combination is not commensurate with the incremental price.

Next, consider a case where a new add-on treatment is combined with an existing monotherapy. Assume that the existing therapy is given every month, and is priced so that the incremental cost of providing each extra month of life is just supported by the added value associated with that life extension. Imagine that combining the add-on treatment with the existing therapy results in, say, patients living an extra (incremental) 6 months, but, this requires 6 months more treatment with the existing therapy. Because the existing therapy is priced at the limit of what the system will pay for each additional month of survival, there is no headroom left for any additional costs associated with the add-on treatment. In the case where the existing therapy is priced at exactly the level that allows its continued treatment to be considered cost-effective, then, assuming some costs associated with administering the new add-on treatment, it would not be considered cost-effective even if it was provided at zero price: hence the seemingly illogical "not cost-effective at zero price" phenomenon. More generally, when existing therapies are priced *close to* the level that allow their continued treatment to be considered cost-effective, there exists very little headroom for any additional costs associated with an add-on treatment This would be true, irrespective of the number of additional months survival the combination therapy produced.

Such a situation occurred when the United Kingdom's (UK) National Institute for Health and Care Excellence (NICE) appraised pertuzumab in combination with trastuzumab and docetaxel for breast cancer [3-5]. Pertuzumab increased survival but was not considered cost-effective even at zero price because all allowable incremental costs were taken up by an increased duration of backbone therapy. Similar findings were present in NICE appraisals of vinflunine for advanced or metastatic transitional cell carcinomona [6,7] and cetuximab for head and neck cancer [7,8], and a previous review in this area undertaken by Danko *et al.* stated that in health systems that estimate cost-effectiveness, "add-on therapies are usually not cost-effective… due to the incremental direct costs of constituent therapies" [1].

High-cost combination therapies present challenges irrespective of whether the value assessment approach uses cost-effectiveness or "therapeutic added value", and irrespective of exactly which costs (direct, indirect, societal) are included and how benefits are measured (disease specific, quality of life). Under any approach, agencies must consider if the outcomes expected from a combination therapy justify overall cost, and the situation can arise where the combination therapy is more effective than the backbone therapy alone, but the combined cost is not considered commensurate, and therefore the treatment is either not recommended by the HTA agency/payer or the add-on therapy is not made available by the manufacturer.

In November 2019 an International Workshop was convened by Bellberry, a not-for-profit organisation that aims to improve the welfare of research participants, with the aim of discussing – and making proposals for addressing – the issues associated with valuing and paying for combination therapies in oncology. Fifty-three attendees representing payers / HTA bodies, industry, patients, clinicians and academics, from Australasia, Asia, Europe, and North America, discussed the issues during the two-day Workshop, facilitated by pre-read materials and a scientific secretariat [2]. Attendees confirmed that combination therapies are presenting major challenges for affordability and patient access in health systems around the world, specifically when *on-patent* treatments are combined, and when *different* manufacturers produce the constituent parts of a combination [2]. The views we express here on how to address these challenges are informed by discussions at the Workshop, a full report of which is available [2].

What Can be Done?

Fundamentally, the challenges around valuing and paying for combination therapies in cancer centre on value for money: the costs of combination regimens are frequently too high, given

their perceived value and a system's willingness to pay. Potential solutions will therefore involve reducing costs, improving value, or increasing willingness to pay.

We are aware of no evidence that society is willing to pay more for combinations as compared with single treatments offering comparable value. We therefore see no good argument for differential willingness to pay for combination therapies, a view supported by discussions at the Workshop [2]. HTA bodies should use their standard methods when assessing combination therapies (and, as is the case for any new treatment, ensure costs and benefits are captured accurately and conduct incremental analyses compared to existing standard therapies).

The Workshop identified various ways in which the value of combination therapies might be improved, for example through altered dosing schedules and treatment durations (including treatment stopping rules), leading to reduced toxicity, improved quality of life, and lower costs. We believe these merit further consideration. But they would require modifications to established approaches to clinical trials and so be challenging to achieve. We therefore consider the most fruitful area for action in the short term is that of costs, and we focus on that in the remainder of this editorial.

If the principle that price should reflect value is accepted, then the price of a treatment should be re-visited when it has a new use, whether that is as a backbone therapy combined with new add-on treatments, or as part of a new combination of existing treatments. It is the inflexibility in prices of pre-existing treatments that results in the lack of "headroom" for costs associated with clinically effective add-on treatments, and this must be addressed. This was recognised by attendees at the International Workshop, but further discussion is required (and was recommended in the Workshop report) [2].

Implementing a system where the prices of pre-existing treatments are amended when those treatments are included as part of a new combination raises practical challenges. Manufacturers will be reluctant to enter price negotiations if the result is a reduced price for indications in which the treatment is already used and accepted as cost-effective. So a form of multi-use pricing is likely to be required, allowing prices to differ for a treatment depending upon the disease area it is being used in, and/or depending on whether it is being used as monotherapy or in a particular combination [1,9,10]. Multi-use pricing has been much debated, with concerns raised (and disputed) around the impact on consumer and producer surpluses [9-13]. In this case we are proposing it be used specifically to enable a lower price to be paid for a backbone therapy when it is in combination use rather than in monotherapy use, enabling patient access to effective combination therapies (provided that they are cost-effective with the revised backbone therapy price). In this situation, allowing multi-use pricing would provide societal benefits.

Multi-use pricing systems may, however, be complicated to run. They would ideally be based on detailed data on the exact use of treatments, but proxy measures may suffice. Whilst the challenges of generating use data may be considered a deterrent, increased use of "real world data" or "big data" is currently being promoted in HTA, and the European Medicines Agency has published draft guidelines on registry-based studies [14]. We see a strong case for using large-scale data-collection systems to help address combination therapy access issues. In the UK, the Systemic Anti-Cancer Therapy dataset is a comprehensive database allowing an understanding of cancer treatment patterns on a national scale [15]. Databases like this could be used to inform the operation of a multi-use pricing system and could also be used to collect information on treatment duration (and potentially the effectiveness of altered dosing schedules and treatment durations) which could inform assessments of value for money.

In addition, if flexible pricing were implemented for combination therapies, prices would need to be determined for each component of the combination. There are methodological challenges in developing a framework for attributing value to constituent parts of a combination therapy. Potentially more problematic, however, is agreeing the roles that companies and HTA/payer bodies can and should play in negotiating and agreeing prices for each component. Competition law may mean that price negotiations between companies about products that are both competitive and complementary are seen as collusion, even if mediated or sanctioned by an HTA/payer body. Based on the discussion at the Workshop, it would appear that views differ between HTA bodies on the extent to which it is appropriate for them to become involved, and it seems likely that different solutions will need to be developed in different jurisdictions to reflect differences in laws, remits and attitudes [2].

Conclusions

The high cost of some combination therapies for cancer is restricting patient access to clinically effective treatments. The problem arises because on-patent treatments are being combined, resulting in clinical benefits but at disproportionately high cost. Price flexibility is needed for all components of a combination, otherwise it remains likely that some clinically useful high cost combinations will fail to meet cost-effectiveness requirements. This is likely to require some form of multi-use pricing. Value attribution frameworks could help to support price negotiations and represent an interesting academic area of research. More discussion is needed of the respective roles of companies and HTA/payer bodies in price negotiations, and of potential legal challenges and ways to address them in different jurisdictions. But, if cross-company pricing negotiations are possible in other industries (for example, round-the-world air tickets), why not in healthcare, where the outcomes will improve societal health?

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References

[1] Danko D, Blay JY, Garrison LP. Challenges in the value assessment, pricing and funding of targeted combination therapies in oncology. Health Policy, 2019;123;12:1230-1236.

[2] Latimer N, Pollard D, Towse A, Henshall C. Challenges in valuing and paying for combination regimens in oncology. Report of an international workshop convened by Bellberry. May 2020. [Available from: https://bellberry.com.au/wp-content/uploads/Meeting-report-final-draft-May-2020.pdf]

[3] National Institute for Health and Care Excellence, *Breast cancer (HER2 positive, metastatic) - pertuzumab (with trastuzumab and docetaxel): appraisal consultation document.* 2013, The National Institute for Health and Care Excellence: London, UK.

[4] Fleeman, N. Bagust A, Beale S, *et al.,* Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer. 2013, LRiG, The University of Liverpool.

[5] National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013 [Available from: http://www.nice.org.uk/article/pmg9/chapter/foreword]

[6] National Institute for Health and Clinical Excellence. Vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract: NICE technology appraisal guidance 272. 2013. London, UK, The National Institute for Health and Clinical Excellence

[7] Davis S. Assessing technologies that are not cost-effective at zero price. Report by the Decision Support Unit, July 2014

[8] National Institute for Health and Clinical Excellence. Cetuximab for the treatment of recurrent and / or metastatic squamous cell cancer of the head and neck: NICE technology appraisal guidance 172. 2009. London, UK, The National Institute for Health and Clinical Excellence. 2014.

[9] Towse A, Cole A, Zamora B. The Debate on Indication-Based Pricing in the US and Five Major European Countries, in *OHE Consulting Report*. 2018, Office of Health Economics: London.

[10] Mestre-Ferrandiz J, Towse A, Dellamano R, Pistollato M. Seminar Briefing 18: Multi-indication Pricing: Pros, Cons and Applicability to the UK. , in *Office of Health Economics: Research*. 2015, Office of Health Economics: London.

[11] Campillo-Artero C, Puig-Junoy J, Segú-Tolsa JL, *et al.* Price Models for Multi-indication Drugs: A Systematic Review. Appl Health Econ Health Policy. 2020;18:47–56.

[12] Chandra A, Garthwaite C. The Economics of Indication-Based Drug Pricing. New England Journal of Medicine. 2017;377.2: 103-106

[13] Cole A, Towse A, Lorgelly P, Sullivan R. Economics of Innovative Payment Models Compared with Single Pricing of Pharmaceuticals. Research Paper. July 2018. Office of Health Economics: London.

[14] European Medicines Agency, Guideline on registry-based studies: Draft. 24 September 2020, EMA/502388/2020. Available from https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-registry-based-studies_en.pdf , accessed 24/11/20

[15] Systemic Anti-Cancer Therapy (SACT) Dataset, National Cancer Registration and Analysis Service (NCRAS), operated by Public Health England. www.chemodataset.nhs.uk, accessed 27/20/2020