Cost-effectiveness of precision cancer medicine-current challenges in the use of next generation sequencing for comprehensive tumour genomic profiling and the role of clinical utility frameworks (Review)

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Abstract. Precision cancer medicine (PCM) is an emerging paradigm in oncology, which includes tumour comprehensive genomic profiling (CGP) to enable molecularly guided therapy. However, cost-effectiveness analyses of PCM are faced with several challenges and, thus, its cost-effectiveness remains unclear. Early trials using only molecularly guided therapy were faced with the challenge of providing adequate measures of outcome, which probably explains the modest treatment benefits demonstrated. Endpoints like the progression-free survival (PFS)2/PFS1 ratio may assist in overcoming this issue. Moreover, specific tumour subtypes appear to benefit more from PCM. Costs associated with next-generation sequencing (NGS) for CGP are decreasing, but targeted therapy itself represents a major cost driver. CGP not only enables prediction of response to treatment, but also resistance, and could thus prevent administration of unnecessary (and costly) therapies. In clinical practice, the presence of clinical frameworks, such as the Recommendations for the Use of NGS for Patients with Metastatic Cancers from the ESMO Precision Medicine Working Group, and the ESMO Scale for Clinical Actionability of Molecular Targets, are essential in appropriately identifying situations where PCM is clinically meaningful, thereby improving its cost-effectiveness.

Contents

1. Introduction

Precision cancer medicine (PCM) is an emerging paradigm in cancer treatment striving to tailor anticancer therapy to the individual patient and treatment scenario. Originally, it referred to targeted or biomarker driven therapy (1). Examples of this approach include the use of monoclonal antibodies against cancers expressing a particular antigen/receptor, such as rituximab in CD20-positive B-cell lymphoma, or the use of tyrosine kinase inhibitors (TKIs) targeting a mutated kinase, such as EGFR-TKIs in lung cancer with EGFR driver mutations. With increasing availability and evolution of high-throughput technologies, such as next-generation sequencing (NGS), the concept of PCM has evolved to include comprehensive genetic profiling (CGP) of individual tumours, in order to identify and target alterations that are patient- and tumour-specific (2). This promise of personalized cancer therapy initially appeared alluring; however, the results of prospective trials have been sobering. The increased costs of

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Abbreviations: PCM, precision cancer medicine; CGP, comprehensive genomic profiling; NGS, next-generation sequencing; TKI, tyrosine kinase inhibitors; PFS, progression-free survival; NSCLC, non-small cell lung cancer; WES, whole exome sequencing; ESMO, European Society of Medical Oncology; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets

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comprehensive molecular tumour profiling for each individual patient and the cost of targeted therapy itself, pose the question of the cost-effectiveness of this paradigm (3). Contrary to the broad application of PCM, streamlining its use in clinical scenarios where it is deemed to be clinically meaningful based on internationally recognised clinical frameworks can be an essential step in increasing its cost-effectiveness.

2. Clinical outcomes

The PCM approach has been tested in several prospective trials to date. The SHIVA trial (4) randomized patients to receive either molecularly guided therapy or the physician's choice. Progression-free survival (PFS) was similar in both arms [2.3 months in the experimental group vs. 2.0 months in the control group (P=0.41)]. Trédan *et al* (5) reported one of the largest series to date, including 2,579 patients with advanced cancers in the ProfiLER trial. Molecularly guided treatment could be recommended for 27% of the patients, but only 6% received targeted therapy, achieving an overall response rate (ORR) of 0.9%. The MOSCATO trial (6) was a single-arm, prospective trial of high-throughput genomics-based targeted therapy in patients with advanced cancers, reporting an ORR of 11%. In 33% of the patients (63/193), the PFS was at least 30% longer compared with previous-line therapy (PFS2/PFS1 ratio >1.3). This ratio is an emerging treatment endpoint in PCM (7), which calculates an intra-patient PFS ratio, by dividing the PFS interval associated with molecularly guided therapy (PFS2) by the PFS interval associated with the last prior systemic therapy (PFS1). The WINTHER trial (8) demonstrated a PFS2/PFS1 ratio of >1.5 in 22.4% of the patients. These modest outcomes may be attributed to intra-tumour heterogeneity, clonal evolution and emergence of resistance mechanisms under treatment with targeted agents (9,10). One important challenge that has been highlighted is to provide meaningful measures of outcome in small-n basket/umbrella trials. Innovative endpoints, like the PFS2/PFS1 ratio, used in the WINTHER and MOSCATO trials show promise in addressing this issue (7). These aforementioned trials represent 'unguided', broad application of CGP in solid tumours. PCM has however revolutionised treatment in specific tumour entities, including non-small cell lung cancer (NSCLC). Furthermore, in other entities, where molecularly guided treatment is not currently international standard, such as pancreatic cancer, performing CGP with NGS achieved a relevant increase in overall survival among patients in whom an actionable molecular alteration was identified in a retrospective register analysis [2.58 years (95% CI: 2.39 to not reached) vs. 1.51 years (95% CI: 1.33-1.87); P=0.0004] (11). Within the MOSCATO trial itself, in the subgroup of patients with advanced biliary tract cancer, treatment with molecularly guided therapy was associated with a lower risk for death (HR=0.29; 95% CI: 0.11-0.76; P=0.008), with an ORR of 33% (vs. 11% in all tumour entities in the study) and a PFS2/PFS1 ratio of >1.3 in 50% of the patients (vs. 30% in all tumour entities in the study) (12). Therefore, it is essential to correctly identify the tumour entities/clinical settings where PCM can lead to clinically meaningful improvements in outcome.

3. Costs

The sequencing of the first human genome in 2003 has been estimated to be between $500 million and $1 billion (13). The ongoing technological advancement in NGS techniques has led to a cost decrease of at least 5 orders of magnitude, and was projected in 2016 to lay <$1,000 per genome in 2020 (13). A meta-analysis of trials conducted between 2005 and 2016 by Schwarze *et al* (14) showed that cost estimates ranged from $555 to $5,169 for whole exome sequencing (WES) and from $1,906 to $24,810 for whole genome sequencing (WGS). In one of the most recent analyses in 2016, Van Nimwegen *et al* (15) calculated a per-sample cost of €1,669 for WGS, €792 for WES and €333 for targeted gene panels.

However, the financial burden of PCM is currently primarily driven by the cost of targeted treatment itself, rather than by diagnostic measures. Pagès *et al* (16) calculated the CGP cost per patient within the MOSCATO trial in France at €2,396, which was found to be only 6% of the total treatment costs; the cost of targeted therapy per patient was €31,269. Characteristically, anticancer drugs (54%) and hospitalizations (35%) primarily accounted for the financial burden. For patients treated with chemotherapy, treatment costs were only slightly lower at €29,183, driven primarily by higher hospitalization costs (+27%), whereas targeted therapy was mostly administered in the ambulatory setting. In conclusion, while the costs of genetic testing are continuously declining, the costs of targeted therapy remain significant and are not expected to decrease. On the other hand, CGP not only enables prediction of response to treatment, but also resistance, thus preventing further application of unnecessary (and costly) therapies (17). Lastly, 'unguided' treatment may also be equally financially burdensome due to the increased need for hospital admissions.

4. Cost-effectiveness

In a recent systematic literature review by Schwarze *et al* (14) in 2018, which discussed the role of WES and WGS in genetic diseases, cancer and infectious pathogens, the authors concluded that available evidence is currently insufficient to draw a definitive conclusion on whether PCM is cost-effective. When estimating cost-effectiveness in broad NGS panels (targeted panels, WES or WGS) in the context of PCM, one is faced with specific challenges. The first concerns evaluating the efficacy of PCM itself. The established measure of efficacy in the era of evidence-based medicine, the placebo-controlled phase III randomised trial, is nearly impossible to apply in the context of PCM. The number of patients included in various umbrella or basket trials in PCM is insufficient to reach significant levels of statistical power for traditional endpoints, such as overall survival or PFS. Thus, Moscow *et al* (2) suggested that '….the clinical implementation of PCM might involve a trade-off between a different standard of evidence for the adoption of new therapies, as is the case in patients with orphan diseases, in exchange for higher levels of precision in the assignment of treatment….'. New clinical trial designs and endpoints, like the PFS2/PFS1 ration in the MOSCATO and WINTHER trials (6,8), are required to better quantify treatment benefit. Furthermore, there may be additional challenges

when addressing the cost-effectiveness of PCM, as identified by Phillips *et al* (18). One such challenge is the difficulty of setting an appropriate comparator for NGS, i.e., single vs. multiple gene testing vs. no genetic testing. A single NGS panel could be used cost-effectively instead of multiple analyses of single genes, for example in NSCLC (19). Moreover, broad NGS panels often result in multiple secondary findings, or variants of unknown significance. Tracking the various cost and outcome trajectories that derive from the clinical significance each of these accidentally identified variants is almost impossible in a cost-effectiveness analysis. For example, accidental identification of a germline BRCA1/2 mutation could lead to risk-reducing mastectomy, initially causing an increase in healthcare costs. However, over time, costs probably would be reduced due to decreased breast cancer incidence (20). This also highlights the challenge of defining the time frame in which costs and outcomes apply. Certain costs, such as data storage or the need for additional tests (germline or family members), are difficult to depict when accompanied by findings of unclear significance. On the other hand, secondary germline data acquired with NGS, including genetic polymorphisms predicting altered pharmacokinetics, may become relevant in future medical situations, and the potential benefits of their knowledge cannot be adequately depicted at the time of NGS testing (18).

5. Clinical utility frameworks

Based on accumulated experience with PCM in the research setting across various cancer types and the currently available arsenal of targeted agents, different types of tumours in which the use of NGS is deemed to be clinically meaningful in daily practice can be identified. Being able to appropriately identify the clinical settings in which PCM is clinically meaningful may be the cornerstone in improving its cost-effectiveness. The ESMO Precision Medicine Working Group recently published a guideline (21) recommending NGS testing in NSCLC, cholangiocarcinoma, prostate and ovarian cancers. While the first critical step is to identify patients who would benefit from NGS testing, the next step is to determine which of the identified variants provide the most appropriate target at the given situation, because, as discussed above, targeted treatment itself is also a primary cost driver. While this obviously requires a great degree of experience and depends on the individual situation, the actionability of any individual alteration itself can be quantified to a certain extent. The ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT) (22) classifies genomic alterations based on the quality of existing evidence supporting their clinical actionability. During clinical decision making, selecting the right patient for broad NGS diagnostics and focusing on variants with better evidence for clinical utility should tip the scale further toward higher cost-effectiveness of PCM.

6. Conclusions

Further advancements in clinical trial design, evaluation of clinical outcomes and, most importantly, the costs associated with PCM are required for adequate assessment of its cost-effectiveness. To the best of our understanding, as targeted treatment costs are unlikely to decrease, it is the declining costs of NGS that may enable broader application of the PCM approach in the future. Additionally, internationally recognised clinical frameworks can aid with appropriate selection of the tumour entity, the clinical setting and the alteration to be targeted. Thus, the economic sustainability and cost-effectiveness of PCM can be ensured and its use in daily clinical practice can be broadened in the near future.

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Ethics approval and consent to participate

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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