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Current practice in and considerations for personalized medicine in lung cancer: From the patient's molecular biology to patient values and preferences

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ABSTRACT

Both at the individual and health system levels, the burden of complex illnesses associated with and which rise in mid- to later life, such as cancer, is expected to increase further. The advent of personalized medicine, or the use of a patient's genetic profile to guide medical decisions, is touted to substantially improve drug tolerance and efficacy and, in so doing, also improve the effectiveness and efficiency of oncological care. Amidst the hype and hope surrounding personalized cancer care, there is increasing concern about its unnecessary, unintended effects especially with regards to the financial burden of targeted therapies using specialty drugs. In this paper, we take a patient-centered perspective on the therapeutic benefits of personalized medicine as well as the limitations of current practice and its psychological and financial toxicities by focusing on advanced-stage lung cancer. We argue that the modest clinical benefits of targeted therapy, premium prices for many specialty drugs and the narrow focus on the genetic constitution of individual patients run the risk of undercutting personalized lung cancer care's contribution to realizing health and non-health outcomes. We discuss the contribution of grading the financial burden of treatment and seamless integration of palliative care as key action areas regarding patients' access to and appropriateness of care given patients' needs and preferences.

Contents

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1. Introduction

With population aging around the world and a greater incidence of cancers and complex illnesses that emerge in mid- and late-life, societal debates are increasingly focused on rapidly rising healthcare costs and the economic burden such costs bring to individuals and their health systems [1]. Personalized, or 'precision', approaches to medicine are widely envisioned as the future of medicine, with an individual patient's genetics at the center [2–4]. In its predictive capacity, personalized medicine has been portrayed by many as a panacea for preventing and reducing the incidence of certain types of disease and, in its clinical capacity, for reducing the need for costly medical intervention once disease has manifested by developing more targeted diagnostics and genetically-compatible pharmaceuticals that can reduce the ineffective use of expensive drugs and minimize side effects and adverse events [3,4].

The impetus for moving towards a more individually-focused outcome-based healthcare system comes not only from developments in personalized medicine that require new ways of thinking about prevention and treatment. It also comes from patients themselves, especially with the rising incidence of chronic and complex illnesses generating a paradigm switch from 'cure' to 'management' [5]. Patient-doctor relations within many health systems are shifting, with growing emphasis on patient involvement in not only maintaining their health but also deciding on their course of treatment once they fall ill. In what is increasingly known as 'individualized' or 'patient-centered' care, doctors first endeavor to inform patients of their conditions and what measures are possible for curing or managing them, and then work with patients to identify their preferences and develop a plan for achievable goals along the clinical pathway [6].

Health systems – with their standardized procedure-based reimbursement systems' focus on controlling isolated issues/indicators [2] – unfortunately, have been slow to acknowledge the whole patient and adapt in ways that recognize his/her autonomy and dignity by supporting his/her goals and preferences. Indeed, so-called 'personalized' approaches to medicine *after* conditions have manifested in patients' bodies remain narrowly medicalized, with patients – quite de-centered – viewed as far more passive agents. Thus, while medical intervention may have the potential to be more tailored genetically to the patient than ever before, the patient remains primarily received as a biological subject. This scenario is particularly evident in cases where patients are confronted by terminal diagnoses, such as with metastatic cancers.

In this paper, we take a patient-centered perspective on the therapeutic benefits of personalized medicine, the limitations of its current practice and its psychological and financial toxicities by focusing on advanced-stage lung cancer—one of the leading causes of death in the world [7]. Most commonly manifesting in people between 55 and 84 years of age, non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancer and diagnosis is frequently made at an advanced stage, resulting in very low survival rates, a substantial symptom burden and more than 50% of patients dying within the first year of diagnosis [8,9]. Yet, despite the eventuality of death, patients with advanced-stage NSCLC do not always have the opportunity to establish treatment goals with their doctors. By default, they instead frequently receive costly, aggressive therapies towards the end of their lives, accessing palliative care and psychological support only in their final days.

2. Personalized cancer care with targeted therapy for NSCLC

An important advance in oncology has been the identification of genetic alterations that function as drivers for a tumor. In lung cancer, this has led to a more nuanced classification of disease progression and, consequently, of patients themselves for purposes of targeted therapy. As such, personalized medicine holds much promise for – and, has already made inroads in – lung cancer care. NSCLC, for example, is a paradigm for multi-marker testing (and targeted therapy) in cancer [10], as it is no longer regarded as a single disease but, rather, as a collection of groups of tumors [11].

Platinum-based doublet chemotherapy is currently the conventional approach to treatment in patients with advanced-stage NSCLC and a good (Eastern Cooperative Oncology Group) performance status (PS of 0–1) [9]. For patients with a PS of 0–1, the median survival time is 9.5 months, and the estimated one-year survival rate is 41%. Among patients aged 70 and over, the estimated one-year survival rate is 35%. For those with a PS of 2, the median survival time with combination chemotherapy is 4.7 months, and the estimated one-year survival rate is 18% [12]. Despite greater treatment-related toxicity, platinum-based doublet chemotherapy shows similar efficacy in elderly patients and it is indicated for those with a PS of 0–2, adequate organ function and no major comorbidities [13].

The molecular characterization of NSCLC contributes valuable information about the patient's prognosis and potential for treatment with molecular-targeted drugs which interfere with specific molecules or pathways related to the proliferation of tumor cells [14]. Depending on the NSCLC patient's histologic subtype, targeted therapy can offer significant clinical benefit over conventional platinum-based doublet chemotherapy when offered to certain patients [11]. Epidermal growth factor receptor (EGFR) mutations and echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) translocations are driver genetic alterations in NSCLC for which molecular-targeted drugs are available, as presented in Table 1.

2.1. Targeted therapies for advanced-stage NSCLC

Compared with conventional platinum-based chemotherapy in patients with EGFR mutation-positive NSCLC, first-line EGFR-tyrosine kinase inhibitor (TKI) therapy has demonstrated improvement in response rates, quality of life, symptoms, and median progression-free survival (PFS) as well as more favorable toxicity profiles—but not overall survival (OS) [9]. Furthermore, almost all non-squamous NSCLC that respond initially to EGFR TKIs eventually relapse and resist further drug treatment [21], leading to the development of second- and third-generation EGFR TKIs [22]. EGFR TKI use began in 2003 with the approval of gefitinib by the US FDA for advanced-stage NSCLC patients for whom all approved chemotherapies failed [23].

In addition to gefitinib, erlotinib is a first-generation EGFR TKI which also has been extensively tested in the first-line setting in the elderly population because of the perceived need for options less toxic than cytotoxic chemotherapy [24]. It is also indicated in patients without an EGFR mutation undergoing second- or third-line treatment [25]. Afatinib has been shown to modestly improve PFS in patients for whom previous EGFR TKI treatment failed [26]. Patients treated with crizotinib, for second (or subsequent)-line use, as compared with those treated with conventional chemotherapy, have been shown to experience significant improvements in PFS (7.7 months vs. 3 months) and objective response rate (65% vs. 20%) [27].

The use of EGFR TKIs according to line of treatment differs between the US and the European Union (EU), however. Gefitinib in the US was limited to second- and third-line treatment after post-marketing studies in 2005 failed to show an overall survival benefit for patients taking it [28]. By contrast, gefitinib is used in all lines of treatment for patients with EGFR mutations in the EU. In England, for example, the National Institute for Health and Care Excellence

Table 1
Molecular-targeted therapies for advanced-stage NSCLC and their companion diagnostics.

Oncogene	Mutation prevalence	Active ingredient	Drug brand name	Year of approval		Monthly cost [20] 2014*	US FDA-approved companion diagnostic
				FDA [18]	EMA [19]		
ALK	7% among Caucasians [15]	Crizotinib	Xalkori	2009	2012	11,571	Vysis 4800 BRAF V600 mutation test
EGFR	20–40% Among Asians; 16% among Caucasians [16]	Afatinib	Gilotrif	2013	2013	6071	Therascreeen EGFR RGQ PCR Kit
		Erlotinib	Tarceva	2004	2005	5233	Cobas EGFR mutation test
KRAS	15% among Caucasians [17]	Gefitinib	Iressa	2003	2009	2066	N/A

* In actual USD; anaplastic lymphoma kinase (ALK); epidermal growth factor receptor (EGFR); Kirsten rat sarcoma viral oncogene homolog (KRAS).

(NICE) recommends gefitinib as first-line treatment for NSCLC only in patients testing positive for EGFR gene mutations and where the manufacturer provides gefitinib at an agreed (fixed) price as part of the patient access scheme [29].

2.2. Molecular testing of lung cancer patients

EGFR mutation can be detected using three different techniques, namely, Sanger DNA sequencing, polymerase chain reaction (PCR) mediated analysis (e.g., Cobas EGFR Mutation Test [22]) and immunohistochemistry [16]. A systematic review of EGFR-TK mutation tests currently available showed that there were no substantial differences between tests in batch size, turnaround time, number of failed samples or cost [30]. Nevertheless, (access to and reimbursement of) molecular testing might serve as a bottleneck for patients' access to targeted therapies, as can be seen in Canada, where there is no provincial funding mechanism for testing that costs CAD400–450 per case (€285–320, £207–233 as of 5 March 2015) [31].

Molecular testing beyond EGFR and ALK is not currently recommended for NSCLC [32]. Kirsten rat sarcoma viral oncogene homolog (KRAS) mutational analysis can serve as a screening test for EGFR and ALK TKI therapy because it is a strong negative predictor for identifying aberration in either EGFR or ALK [11]. In France, for example, where all lung cancer patients are tested for EGFR and ALK mutations, the presence of KRAS mutation in patients' tumors rendered them ineligible for anti-EGFR treatments [33]. In 2011, it saved EUR69 million by not treating 15,000 EGFR-negative patients (of a total of 16,724 lung cancer patients) with an eight-week course of gefitinib [34]. Guidelines in the US, however, do not recommend KRAS mutation testing as a sole determinant of EGFR TKI therapy [35,36]. As such, unlike testing for EGFR and ALK mutations, the utility of routine clinical testing for KRAS mutation is under debate [37].

3. Patient preferences for personalized cancer care

At present, actionable mutations in NSCLC only account for a small subset of the NSCLC patient population. Moreover, none of the current targeted treatments for advanced-stage NSCLC offers clinically meaningful outcomes in terms of OS [38]. Whereas the absence of benefit in OS has been presumed to result from the crossover of the vast majority of patients receiving initial chemotherapy to an EGFR TKI at progression [39] – where OS is regarded as meaningful end-point in NSCLC rather than PFS – the benefits of targeted therapies in NSCLC are modest. Given the high price tag of targeted therapies, what can be done to maximize the health, economic and psychological benefits of personalized medicine both for the individual patient and society at large?

Like health systems (e.g., the UK's NHS with its patient access scheme), individuals are found to be willing to pay only a fraction of TKIs' market price [40]. Indeed, affordability is a concern not just at the health system level but also at the micro (i.e., patient) level, if not more so, as high treatment costs – of which drugs represent a significant percentage of direct expenses – may threaten patients' (and their families') financial stability and security. And some patients are luckier than others. People living with cancer in the US, for example, are three times more likely to file for bankruptcy than people without cancer [41]. In 2010, mean monthly net costs were USD7710 (€7084; £5160 as of 4 March 2015) for elderly lung cancer patients in their last year of life [42]. Yet the poverty threshold for a one-person household for people aged 65 years and over was USD10,458 (€9608; £7000 as of 4 March 2015) [43].

To deal further with the issue of high (anti-)cancer drug costs, the Cancer Drugs Fund was set up by the UK government in 2011 to commission cancer drugs not approved by NICE and not available within the NHS England. However, it has been criticized as inequitable and cost-inefficient [44]. Given budget limitations, system-level disinvestments elsewhere (e.g., within the clinical pathway, between conditions, across patient groups, etc.) will be made just as at the individual patient level, where individuals and families might have to – and do – choose between cancer treatment and paying for basic necessities. Patients deal with the financial burden of their treatment in various ways, from taking sub-optimal medication or under-medicating [45] to crossing borders to refill their prescriptions [46] to discontinuing their medication altogether [47]. As many as 61% percent of elderly Medicare (Part D) beneficiaries on erlotinib, for example, either delayed or stopped medicating due to a daily out-of-pocket (OOP) payment of USD28.35 [48].

3.1. Affordability: Grading the financial burden

The financial burden of medical treatment has been alluded to as 'financial toxicity', and critics advocate for it to be discussed alongside the physical side-effects of medication and therapies when addressing treatment options with patients in a patient-centered scenario [49]. A systematic review of the literature on the unmet needs of newly diagnosed older cancer patients undergoing active cancer treatment found that, while the most common needs varied by study, psychological and information needs were primary [50]. As such, uncomfortable though it may be, consideration of the individual and collective financial burden of targeted treatment – a central feature of personalized medicine – is imperative when talking about the benefit and consequences of patient-centeredness in medicine. In understanding the values and preferences of individual patients, optimal patient-centered treatment plans would be arrived at not *for* but, rather, *with* patients and their families [51]. As presented in Table 2, the financial burden of treatment can be graded according to OOP expenditure and health insurance status.

Health insurance coverage does not automatically translate into financial protection from medical-related expenditures since mechanisms such as co-payment and co-insurance are in place to control moral hazard and manage spending at the meso (i.e., health plan, health insurer) and macro levels. These lead to expenditures which could be substantial and even catastrophic where such

Table 2
Financial burden of treatment grading based on out-of-pocket expenditure and income.

Grade (degree of financial burden)	Description
1 (Mild)	Out-of-pocket for drug costs not covered by health insurance and supplementary insurance premium is 5–10% of disposable household income
2 (Moderate)	Out-of-pocket for costs not covered by health insurance and insurance premium is 10–20% of disposable household income
3 (Significant)	Out-of-pocket for drug costs not covered by health insurance and supplementary insurance premium is 20–30% of disposable household income
4 (Severe)	Out-of-pocket for drug costs not covered by health insurance and supplementary insurance premium is 30–40% of disposable household income
5 (Catastrophic)	Out-of-pocket for drug costs not covered by health insurance and supplementary insurance premium is >40% of disposable household income

spending makes for a substantial share of a household's finances [52]. The higher the degree of financial burden, the greater will be emotional and psychological stress on patients [53], the higher the risk of opting for sub-optimal medication and the greater the need for support. In countries with limited welfare benefits for disability or unemployment, reduced income signifies that the financial burden of treatment will be substantial. Early retirement implies that patients rely on pensions to cover daily necessities as well as their medical bills not covered by age-linked medical benefits, such as Medicare in the US. Even though patient assistance programs can be helpful, the process for applying to these programs can be bureaucratic, thus limiting their viability as a resource [54].

The financial burden grading while prepared specifically for targeted treatment can be extended to include other care-related costs, both direct and indirect. Indirect costs include patients' and care-givers' lost wages and travel not covered or compensated by insurance, which can be substantial especially in health systems that do not reimburse these costs or only partially reimburse indirect costs. However, this paper's focus on targeted drug therapies is motivated by the particularly high cost of treatment compounded by the premium prices of specialty drugs with which both patients and systems alike are grappling [33]. The practice of medication tourism – indeed of medical tourism, in general – highlights the struggle of patients in accessing healthcare at home when what is available is unaffordable [46,55].

3.2. Appropriateness: Palliative care and the clinical pathway for the patient

In spite of their futility, cost and toxicity, both conventional and personalized second- and third-line therapies are frequently prescribed for treating aggressive, advanced cancers [56]. Such therapies may extend patients' lives by a few more weeks or months, but they also may reduce patients' quality of life in the time they have left in inpatient care instead of being at home, and can place significant financial and emotional burden on them and their families, depending on the health system in which they are located [57,58]. Consequently, patients with lung cancer have high levels of unmet needs, especially regarding psychological/emotional and medical communication linked to dealing with concerns about both their own and their family's fears and worries [59].

Patient-centered cancer care must respond to these needs and reflect patient values and preferences along the continuum of care in order to deliver the desired and meaningful benefits for patients, their care-givers and the health system that supports them. This is illustrated by a study of cancer patients receiving either early palliative care integrated with ongoing oncology care or receiving only standard oncology care, which has shown that patients receiving early palliative care had a better quality of life and less depression and were less likely to receive futile treatments and aggressive care at the end of life [57]. Despite receiving less treatment at the end of life, patients receiving early palliative care lived 2.7 months longer than those receiving standard care. Palliating deteriorating patients should not be seen in opposition to the drive to sustain life for as long as medically possible [60]; rather, it should be seen as a component of healthcare that is compassionate and sustainable.

4. Beyond current practice and its narrow medicalized view

In spite of scientific strides in personalized medicine, challenges in personalized cancer care continue. Whereas personalized lung cancer care has delivered desirable benefits for some, meaningful benefits in terms of gains in OS are still lacking [38]. The individual patient continues to be reduced to little more than his/her molecular profile yet the significant costs of targeted therapies threaten the financial well-being of patients and their families and strain the coffers of health systems [53,56]. Many patients with newly diagnosed metastatic NSCLC hold inaccurate perceptions of their prognoses and plan in accordance with those perceptions [61]. As a result, palliative care is poorly integrated in the clinical pathway and far from being an integral part of the care continuum—if it is included at all [62,63].

While the science is advancing, healthcare industry players (e.g., pharmaceutical companies) and payers (e.g. insurers and governments), especially in multi-payer systems, have been reluctant to develop and cover predictive and targeted diagnostics and drug therapies due to insecurities over their own financial interests [64,65]. Transformation at all levels of the health system – including not only revolutionizing the ways in which predictive testing, diagnostics and drugs are developed and financed but also medical practice itself – is needed to address these challenges [56]. Switching, for example, from a primarily standardized procedure-based reimbursement system for practitioners to a more individual patient-focused outcome-based system has the potential to induce greater efficiency and efficacy. Furthermore, payers, through their standardized activity-based reimbursement practices, also continue to favor high-level medical intervention over enabling doctors to hold conversations with their patients in order to fully discuss treatment consequences and to establish their treatment preferences and plans. Indeed, intervention is also more readily financed than multi-disciplinary palliative care programs and integrated care schemes despite growing evidence of their individual and societal benefits and cost savings [58,65].

Especially in cases of short life-expectancy and co-morbidity, standardized medicalized approaches in the practice of personalized medicine, as we have demonstrated here with our review of approaches to advanced-stage NSCLC treatment, ignore the flexibility necessary to respond to individual patients' needs, preferences and coping strategies in ways that may require making trade-offs relative to extending life, managing symptoms and pain, and maintaining physical and mental independence as well as social functioning [5,65]. Such flexibility may help to "mitigate unnecessary and burdensome personal and societal costs" [57, p.740]. Outcome-based reimbursement models can contribute to incentivizing the development, pricing and use of targeted therapies while mapping treatments in terms of outcomes relative to cost and personal objectives will help patients and physicians decide on an optimal treatment plan [66,6]. In addressing the reality of personalized lung cancer care today, we can better ground and realize hopes for the personalized and patient-centered medicine of tomorrow.

Contributors

PMC conceptualized the paper, wrote the initial draft, contributed to the revision and completion of the manuscript and approved the final submission. MO reviewed and revised the initial draft and contributed to the revision and completion of the manuscript and approved the final submission. The authors declare that the manuscript has been submitted solely to the Maturitas and that it has not been previously published, either in whole or in part, nor have the findings been posted online.

Competing interest

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