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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

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