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Path-breaking target therapies for lung cancer and a far-sighted health policy to support clinical and cost effectiveness

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Abstract
The purpose of this paper is to analyze the radical innovations to treat lung cancer, which are generating a revolution in clinical practice, in order to provide fruitful health policy implications. The finding shows an allometric process of scientific growth of target therapies: disproportionate knowledge growth of the new anticancer drug (Gefitinib) in relation to the standard platinum-based chemotherapy. These ground-breaking target therapies for advanced non-small cell lung cancer (NSCLC) may replace standard chemotherapy approaches, which might enter into a maturity phase in the not-too-distant future. The current debate concerns some uncertainties about the efficacy, the long-term effects of these radical innovations on carcinogenesis and the high cost of these new anticancer drugs for healthcare system. Nevertheless, these innovative treatments generate several benefits in terms of higher survival and quality of life. The development of path-breaking target therapies for NSCLC and the efficiency of personalized healthcare system should be based on the understanding of cancer biology, *E*-health system and chemoprevention (e.g. early stage biomarkers) to improve stratification of patients and the precision of first-line target therapies: this strategy may increase the fruitful effects of new multi-inhibitors blocking agents and their cost

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effectiveness; in addition, it is also important a long-run systemic evaluation of costs, based on clinical and economic monitoring of patients to support a far-sighted health policy.

Introduction

Lung cancer is one of the main diseases in several developed countries and a leading cause of cancer death – both sexes – worldwide (*cf*. [42], p. 259; [52], p. 1067 ff). In particular, about 80% of cases are represented by Non-Small Cell Lung Cancer (NSCLC), which is linked to several risk factors, such as smoking [7], passive smoking [52], air pollution (*cf*. [47], *passim*), *etc*. The current therapeutic treatments of advanced Non-Small Cell Lung Cancer (NSCLC), based on traditional chemotherapy agents (such as cisplatin and gemcitabine; carboplatin and paclitaxel, and so on), tend to have low efficacy, which is confirmed by the fact that the mortality rate is still high (24.8% ASR-W; Incidence lung cancer 31.3 ASR-W)[2] in comparison to Breast (Mortality 15.3%; Incidence 66.4), Colorectum (Mortality 12%; Incidence 30.1%) and Prostate cancer (Mortality 10.5%; Incidence 61.7%). The purpose of this paper is to analyze the current pathway of vital radical innovations to treat NSCLC, which are generating a revolution in clinical practice. As these path-breaking anticancer drugs can lead to longer, better, and healthier living, some vital health policy implications for improving healthcare system are discussed [58,19,15–17,24,26].

The analysis of this critical research field can shed light on fruitful radical innovations for NSCLC and their socio-economic consequences on healthcare system in order to support clinical and economic (cost)-effectiveness of personalized medicines [63].

Background

Lung cancer is a: "Cancer that forms in tissues of the lung, usually in the cells lining air passages" (as defined by the [48]). Lung cancer can be either small cell lung cancer or non-small cell lung cancer (NSCLC), with the latter representing about 80% of the cases. The median age at diagnosis for cancer of the lung and bronchus is about 71 years of age (*cf*. [34]) and surgical resection (*e.g*. Thoracotomy) is the most suitable curative treatment when the NSCLC is at its early stage [37,64].[3] Mitsudom ([45], p. 101) claims that: "lung cancer is a major cause of cancer-related mortality worldwide" (*cf*. also [51]). In fact, the five-year survival rate of patients is about 2–10% with the current treatments based on chemotherapy agents (see [54], p. 1; [42], p. 259; *cf*. also [47]). In particular, gemcitabine and cisplatin-based therapy is the reference treatment for advanced NSCLC, but these traditional chemotherapy agents are now in therapeutic competition with path-breaking target therapies based on continuous scientific breakthroughs in converging genetics, genomics, and proteomics [21].[4] As a matter of fact, the target cancer therapies are: "drugs or other substances that block the growth and spread of cancer by interfering with specific molecules involved in tumor growth and progression" (as defined by the [48]). Molecular biology and genetics lay the groundwork for target therapy of lung cancer (Figure 1).

Vital scientific breakthroughs in converging research fields (genetics, genomics, proteomics) have shown that cancer cells display self-sufficiency of growth signals through the accumulation of genetic and epigenetic changes (*e.g*. Epidermal Growth Factor: EGF). The EGF acts by binding with high affinity to Epidermal Growth Factor Receptor (EGF-R) on the cell surface and by stimulating the intrinsic protein-tyrosine kinase activity of the receptor, which ultimately leads to cell proliferation. The presence on lung cancer cells of EGF-R, identified by biomarkers,[5] is important to understand patient differences and a precondition for selecting effective treatments based on personalized medicine in order to block this cancer-specific target (*cf*. [63]). The *first generation of target therapy for lung cancer* is due to the discovery of the EGF-R blocking agents Gefitinib and Erlotinib that has generated two main radical innovations: Iressa® (based on the blocking agent Gefitinib) by AstraZeneca Company (UK-Sweden) and Tarceva® (based on the blocking agent Erlotinib) commercialized by the Roche Group (Switzerland).[6] These target therapies are generating a revolution in therapeutic treatments of NSCLC with EGF-R since they block specific enzymes and growth factor receptors involved in cancer cell proliferation ([45], pp. 101–102). In particular, these target therapies are called signal transduction inhibitors (EGF-R tyrosine kinase inhibitors), which represent ground-breaking anticancer drugs easily administered, in general, as one pill per day (also at home), unlike standard platinum-based chemotherapy for lung cancer (such as Cisplatin associated to gemcitabine for adenocarcinoma of the lung) that is administered intravenously at the hospital for treatment of solid malignancies [23].

[2] Age-Standardized Rate-ASR (W): the age-standardized rate is the rate a population would have if it had a standard age structure. The rate is the number of deaths per 100 000 persons per year. *Data Source*: [31] (IARC) Section of Cancer Information (5/7/2011), http://globocan.iarc.fr/.

[3] James et al. ([37], p. 1672) show that: "many low-income adults… believed that surgery worsens cancer, causing it to metastasize and… expressed reluctance or concern about surgery to treat cancer, because they believed it would worsen their health".

[4] *Genetics* studies the molecular structure and function of genes in the context of a cell or organism. *Genomics* is a discipline in genetics which studies the genomes of organisms. In particular, it deals with the entire DNA sequence of organisms and fine-scale genetic mapping. *Proteomics* is the systematic analysis of protein profiles of tissues and parallels the related field of genomics.

[5] " 'A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic intervention' " (National Institute of Health, as quoted by [2], p. 204)

[6] The literature is vast and not fully cited here, but a good list of references is found in [27], pp. 262–263 and pp. 271–274 and Coccia [23].