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# The new drugs advent: clinical or economic outcomes?

E. De Maio[1], F. Perrone[1], G. Bisagni[2] & C. Boni[2]

[1]*Clinical Trials Unit, National Cancer Institute of Naples, Naples;* [2]*Oncologia Medica, Azienda Ospedaliera, Reggio Emilia, Italy*



Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related death in both men and women. Despite the introduction of newer cytotoxic agents during the last decade the survival rates still remain low. New strategies are clearly needed to improve treatment outcomes.

Chemotherapy is under investigation as neoadjuvant and adjuvant strategy in early stage, and same progress has been achieved in the treatment of locally advanced and metastatic disease; however treatment outcomes for NSCLC are yet to be considered disappointing.

New hope comes from improved knowledge of tumour biology and mechanisms of oncogenesis, with identification of several new potential targets.

Randomized studies conducted over the past decade have shown that cisplatin-based chemotherapy provides a survival advantage over supportive care alone, that two drug chemotherapy regimens are superior to single agent regimens, and that two drug combinations should contain at least one new agent (gemcitabine, paclitaxel, vinorelbine, docetaxel).

Advances in our understanding of cancer biology have led to the discovery of several potential molecular targets and to the development of novel agents that, unlike conventional cytotoxic agents, specifically target tumour cells.

Three such agents are the small molecules, inhibitors of the intracellular tyrosine kinase, gefitinib (G) and erlotinib (E), and the monoclonal antibody anti-EGFR cetuximab, that are being extensively evaluated in NSCLC. EGFR-inhibitors demonstrate significant clinical activity in approximately 10–20% of pretreated NSCLC patients [1, 2]. However, four large phase III randomised, placebo-controlled trials of G and E in combination with standard platinum-based first-line chemotherapy failed to show any survival benefit in patients receiving the experimental drugs [3–6]. Possible reasons include patient selection, drug dose or scheduling, trial design or other factors. Active research is ongoing to improve the efficacy of EGFR inhibitors as monotherapy or in combination with other treatment modalities.

A major concern with the clinical employment of new drugs is the economic burden for the society due to the increased costs of the therapy. Cancer is among the most significant contributors of health care spending in the United States. The National Institute of Health estimated its cost in 2002 at $171.6 billion, $60.9 billion of which was attributed to direct medical costs, $15 billion of which to indirect morbidity costs and $95 billion to indirect mortality costs [7]. Lung cancer in particular is estimated as the second highest cost pathology among seven other analyzed cancers in a retrospective matched-cohort analysis [7]. The mean monthly costs for antineoplastic drug therapy-related office-visits being US$553 and the incremental monthly direct costs US$6181. It is important to note that none of the new biological agents recently developed for lung cancer were included in this analysis.

Clearly, the cost of new drugs raises crucial moral and policy questions [8]. Indeed, much attention is being paid to economic analyses as an instrument for establishing a formal link between costs of therapy and outcomes, to create a rationale basis for approval and commercial distribution of new drugs. Furthermore, clinical trials have been designed to evaluate both clinical and economic outcomes for new drug [9–11] and many countries, like Canada and Australia, require evidence of safety, efficacy and cost-effectiveness (CE) before they approve a new drugs for routine clinical use [12, 13].

However, pharmacoeconomics analyses are a complex, and their practical use is not easy. Hill et al. [14], infact, describe problems with the evaluation and the interpretation of 326 submissions to the Department of Health and Aged Care (DHAC) for funding made under the Australian Pharmaceutical Benefits Scheme. Out of 326 submissions, 218 (67%) were considered to present 'serious problems of interpretation'. Sometimes no randomized controlled trial (RCT) was available or the RCTs were of poor quality or low power. Other problems were found in the analysis of the interpretation of the trial results, uncertainty about choice of comparator or inappropriate comparator. Similar methodological pitfalls with pharmacoeconomic analyses were also found in Italy [15] with the experience of the Comitato Interministeriale Programmazione Economica (CIPE) of the Italian Ministry of Health (the structure responsible for national drug reimbursement negotiations).

Other limitations and source of bias of the pharmacoeconomic analyses are worthy of interest. Friedberg et al. [16] investigated the financial conflict of interest of economic analyses of oncologic drugs and showed that pharmaceutical company sponsorship of economic analyses is associated with reduced likelihood of reporting of unfavourable results over noprofit-sponsored studies (5% versus 38%, respectively, $P = 0.04$).

Therefore, it is normal to look with suspicion at such analysis and even if the publication of guidelines [17] has provided an important contribution to standardizing CE research, some methodological points still remain unclear.

One way to improve the credibility of economic analyses, suggested by the editor of JAMA, is promoting full disclosure of all financial interests, conducting more prospective pharmacoeconomic analyses (in conjunction with phase 3 trials) and for the editors of the medical journals to favour prospective, naturalistic, real-word and pragmatic RCTs [18].

Cost analysis represents only one aspect, an important one, connected with the use of new expensive drugs; the other must consider the impact of the new drugs on the outcomes, designed for evaluating the activity and efficacy of a new agent.

United States statutes require that drugs must demonstrate to be effective with an acceptable safety profile in adequate and well controlled clinical studies, as the basis for marketing approval.

Studies must also provide sufficient informations to define an appropriate population for treatment with a drug, and describe the safety profile and the intended use of the agents.

With respect to oncologic drugs, safety usually implies a risk/benefit assessment, and the acceptable ratio might vary for different diseases, patients' population, or stage disease.

Demonstrating the effectiveness of a new agent usually requires a demonstration of clinical benefit in a defined patients' population.

The term clinical benefit can be interpreted in a number of ways but is commonly accepted to mean that the agent demonstrates an improvement in survival compared with no therapy, equivalence or non inferiority to a know effective treatment, or, in same case, a clear improvement in time to disease progression and/or reduction of toxicity and/or improvement of symptoms or QoL for the patients.

Speaking about clinical outcome, it is important to define and analyse the possible primary endpoints, like survival, quality of life (QoL), time to progression (TTP), or surrogate endpoints, like response rate (ORR).

Improvement in survival is generally considered to be the gold standard for drug approval. It is an unambiguous end point that is no subject to investigator bias or interpretation.

It can be assessed easily, frequently, and without reliance on tumour measurements of any kind.

In any ways, survival also provides a clear risk benefit assessment of a new therapy.

Assessment of patient Qol is a potential clinical trial end point, because it provides information from the patient's perspective about the clinical benefits of treatment.

Increasingly TTP of disease has been proposed an acceptable end point for cancer clinical trials. Like survival, TTP includes all patients in the primary efficacy analysis and has the advantage of achieving the trial end point sooner.

ORR is clearly evidence of anti tumour activity and is a surrogate of clinical benefit. ORR has the advantage of being an early clinical trial end point. Assessment of response duration is as important as measurement of response rate.

A review was recently published to summarize the end points used by the United States Food and Drug Administration (FDA) to approve 71 Oncology new drug applications over a 13-year period [19]. The FDA granted either regular marketing approval or accelerated marketing approval. Regular approval was based on end points that demonstrate that the drug provided a longer life, a better life or a favourable effect on an established surrogate for a longer life or a better life.

Accelerated approval was based on a surrogate end point that is less well established, but that is reasonably likely to predict a longer or a better life. End points other than survival were the approval basis for 68% (39 of 57) of oncology drug marketing applications granted regular approval, and for 100% (14 of 14) of applications granted accelerated approval.

In conclusion, these new therapies are a real promise of the cancer therapy. Presently they are used, or recently approved, in advanced stages of solid tumors (lung, colon, breast, pancreatic cancer) and for some of these the survival gain is so little to be almost of no human interest. To be considered as a true 'therapeutic breakthrough', and to justify the dramatical raise in the costs, new drugs should produce relevant improvement of survival or progression free survival, or have a better toxicity profile, if the efficacy is the same, or be active in a pathology refractory to the conventional therapies.

Well-conducted CE analyses can be useful and should be performed to support decision-making. For very expensive drugs, a re-evaluation in terms of late toxicity, efficacy and costs can be recommended [20]. Such 'outcome research' studies can be used to estimate the real effect of the drug in the clinical practice.

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