Measuring the cost of chemotherapy is important, but it is not enough

Most therapeutic innovations in oncology currently induce limited improvements of the expected health outcomes while they are associated with an important increase in costs and toxicity of treatments. This trend indicates that technical progress in this field follows a law of diminishing returns: increased resources have to be committed to produce one additional unit of outcome, like an additional year of survival for cancer patients. Economic assessments and cost-effectiveness considerations are consequently attracting a growing attention in public debates about adoption, diffusion and regulation of new treatments.

Cost-effectiveness analysis (CEA) and its derivative cost-utility analysis (CUA) are methods of summarizing information on the relationship between resources, measured in monetary terms, that are expended on health interventions, and the health outcomes, measured in numerical units, as a change in health or functional status that result from these interventions [1]. The resulting ratios are commonly expressed as cost per statistical life year saved in CEA and cost per quality-adjusted life year saved in CUA. The comparative analysis of various interventions consists in maximizing the total aggregate health benefits obtained from a given level of available resources or alternatively in minimizing the cost of achieving a given health goal. In the context of potentially controversial decisions about the adoption of costly innovations, providing decision makers with a more accurate information about the cost-effectiveness of innovative procedures may indeed influence the decision process, at various levels: decisions of public or private health insurance schemes to cover costs of the procedure, regulatory decisions of public agencies, prescribing decisions of individual clinicians and acceptability of treatment by individual patients [2].

The paper by Weycker et al. [3] describes an economic evaluation of the cost of neutropenic complications of chemotherapy, on the basis of data from a USA health care claims database. Costs of neutropenia are an important component of total costs associated with chemotherapy, since neutropenia is a common toxic effect of chemotherapy, inducing high rates of morbidity and mortality [4]. The treatment of neutropenia usually requires patients’ hospitalizations, and inpatient stays often account for the largest proportion of total costs of managing cancer patients. It has long been established that this relationship between episodes of neutropenia and longer durations of hospital stays, explains why neutropenia is a major contributor to total costs of chemotherapy [4–6]. The paper by Weycker et al., however, points out that costs of neutropenic complications may have been underestimated by as much as 40% in previous economic assessments. Part of this discrepancy between results of this paper and previous research may be due to methodological differences. Data based on the insurance claims are representative of charges for the payers who reimburse costs of care but do not always reflect the true opportunity costs of medical care as often measured in cost-effectiveness studies on the basis of detailed analysis of physical units of resources used by a medical strategy [7]. Moreover, it is unclear to what extent the sample used by Weycker et al. is fully representative of the whole scope of cancer patients treated by chemotherapy. In particular, very few patients in their sample had received hematopoietic growth factors as a supportive care treatment, while the use of prophylactic granulocyte colony-stimulating factor is known to decrease the risk of febrile neutropenia, and often induces net savings in spite of its high-unit cost [8]. On the contrary, indirect costs, which represent the costs of time lost from work and decreased productivity due to the disease are not included in the data used by Weycker et al. which certainly leads to significant underestimation of true economic costs of neutropenia.

A recent study evaluated that indirect costs account for as much as half of the total supportive care costs when febrile neutropenia is managed in the outpatient setting, and about one-fifth when it is managed in the inpatient setting [9].

The second paper [10] in this issue of *Annals of Oncology* is a CEA comparing docetaxel versus paclitaxel for the treatment of metastatic breast cancer in patients with prior exposure to anthracyclines. This population-based study is consistent with the results from a randomized phase III trial [11] that already showed that docetaxel provides significantly better survival compared with paclitaxel in this group of patients. The CEA carried out by Vu et al. concludes that each additional month of survival had an incremental cost of US$2434. Such incremental ratio may be considered cost-effective in most developed countries, such as the United States, France or the UK if one accepts the pragmatic criterion that strategies producing an additional life year for less than twice the gross domestic product per capita should be considered cost-effective. The authors do not explicitly compare their results to those of previous economic assessments of taxoid agents for chemotherapy in advanced breast cancer [12–16]. Although such comparisons may be difficult due to an absence of standardization across studies in both measures of outcomes

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and costs used, these studies comparing docetaxel and paclitaxel resulted in similar findings, as the incremental cost-effectiveness ratios fall within moderate levels. In addition, some intrinsic methodological limitations of the study by Vu et al. [10] imply some need for caution in interpretation from a decision makers’ point of view. In particular, because the study was retrospective, groups of patients are not comparables in respect to some major clinical characteristics, such as hormonal receptors which are known to be important prognosis factors [17, 18]. Moreover, the follow-up period is not identical between groups, which may induce a bias in the cost-effectiveness comparison. These limitations have been partly controlled for through well-performed sensitivity analyses that varied an extensive range of values for both effects and costs, and consequently increased the robustness of the authors’ conclusions.

In any economic evaluation of therapeutic strategies, true costs and effects cannot be known with absolute certainty because they are estimated from a particular patients’ population. In recent years, economic evaluations have been more and more associated with prospective randomized clinical trials, providing stochastic data on both costs and effects of alternative medical strategies at the level of individual patients. Thus, it becomes possible to handle uncertainty in the estimation of the incremental cost-effectiveness ratio, through the building of confidence regions for this ratio. Various methods for calculating such confidence regions have been explored in the literature such as Taylor’s method, parametric and nonparametric bootstrap methods and Fieller’s method [19]. In a recent study, evaluating the impact of high-dose chemotherapy for advanced breast cancer patients [20], adding a single course of high-dose chemotherapy led to a clinical benefit in terms of disease-free survival for an additional cost that seems to be acceptable, considering the point estimate of the cost-effectiveness ratio. Properly handling the uncertainty associated with the ratio, however, showed that the upper bounds of the estimations would lead to quite different conclusions. In such cases, handling of uncertainty in economic analysis becomes especially important in order to guarantee the robustness of the estimations and minimize the risk of devoting too much resource for a limited improvement.

In cancer care, as in many other fields, medical decision is often confronted to situations in which innovative treatments, which are evaluated through randomized clinical trial, fail to demonstrate a significant advantage in terms of overall survival but may offer other benefits for patients by reducing or delaying the risk of relapse. In practice, this situation arises in many empirical studies as clinical trials are often designed to detect small differences between treatments and medical innovations, as already mentioned, are associated with decreasing returns. The choice of the efficacy criterion therefore tends to become crucial for decision making. Since patients should be more involved in decision making about treatments, quality-of-life (QoL) studies are strongly needed within the context of economic evaluations of innovative treatments of cancer disease. Future economic studies should incorporate this QoL component that could not be practically included, due to their retrospective designs in the two papers presented in this issue of *Annals of Oncology*.

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