Health and Quality of Life Outcomes

Commentary

Clinical and Outcome Research in oncology The need for integration

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Abstract

Cancer is one of the main healthcare problems in Europe. Although significant progress has recently been made, long-term survival is still disappointing for most common solid tumours.

The explosion of information has strengthened the need to create and sustain coordinated interaction between technology, biology, clinical research, clinical practice and health policy. A simple process based on automatic and passive translation from bench to clinical research and eventually to the bed side is usually assumed but cannot be taken for granted.

A critical role might be played by Outcome Research (OR), defined as the discipline that describes, interprets, and predicts the impact of various influences, especially interventions, on final endpoints (from survival to satisfaction with care) that matter to decision makers (from patients to society at large), with special emphasis on the use of patient-reported outcomes (PRO).

Recently, under pressure from several parts of society, the FDA, recognizing the need for faster drug approval, has modified existing regulations and created new rules to allow anti-cancer drugs to be approved more quickly and, in certain but quite common circumstances, single arm trials and surrogate endpoints to be used as measures of clinical benefit. In this context, the faster approval process may lead to drugs being marketed without there being a complete picture of how effective or safe they are.

The FDA move to speed up drug approval, together with the use of not fully validated surrogate endpoints, give OR the unique opportunity to help understand the value of drugs that have received accelerated approval. Despite this opportunity, OR has yet to demonstrate its role in this specific setting and provide proof of the validity, reliability and added value of its primary endpoint measures when evaluated in a broader context.

The implementation of lines of OR in the development and evaluation of anti-cancer drugs hinges upon the availability of specific knowledge, methods, instruments and resources and upon their appropriate integration in the mainstream of clinical research. In the USA specific interdisciplinary projects have been launched by the NCI. In Europe there is a lack of such initiatives.

The correct placement of OR in the anti-cancer drug development process will guarantee the highest possible standard of validity and reliability of OR at European level and better integration of both translational and outcome research in the mainstream of clinical research into anti-cancer

drugs, thus speeding up the introduction of the results of patient-oriented translational clinical research into clinical practice.

Introduction

Cancer is one of the main healthcare problems in Europe. Although significant progress has recently been made in understanding the molecular factors underlying the development of cancer and the improvements achieved in response rates with new drugs, long-term survival is still disappointing in most solid tumours.

The sequencing of the human genome, the increasing availability of biotechnological approaches, the explosive growth of genetics-based biomedical research, have all rapidly expanded the evidence that large numbers of genes (or rather the proteins that they code for) may influence the activity and tolerability of "traditional" drugs". These facts, together with the introduction of "novel" anticancer drugs based on innovative concepts, have greatly increased our knowledge, but these gains have not translated into clinical benefit for patients [1]. This explosion of information has also strengthened the need to create and sustain coordinated interaction between technology, biology, clinical research, clinical practice and health policy [2].

A simple process based on automatic and passive translation from bench to clinical research and eventually to the bed side is usually assumed but cannot be taken for granted. There are three critical steps from the identification of new targets to putting a new drug onto the market. The first concerns the integration of new bio-technologies in a wider context, the second the translation from basic research to early clinical research, and the third the evaluation of the clinical incremental value of new health interventions and its prompt delivery to clinical practice.

Ideally, Translational Research (TR) deals with the first two critical aspects. It is defined as the process of translating findings derived from basic science to the development of a new understanding of the disease mechanism, diagnosis and therapeutics [1]. It implies a bi-directional process, utilising knowledge of human biology to develop and test the feasibility of cancer-relevant interventions in humans and/or determining the biological basis for observations made in individuals with cancer or in populations at risk of cancer. In oncological settings, TR is usually implemented by creating a "functional" bridge between scientists working in the field of basic research and researchers involved in the early phases (phase I-II) of clinical research through ad hoc collaborative efforts. Small but multidisciplinary teams are assembled, the contribution of each member being based on individual skills. As a result, it is now increasingly common in early clinical trials to see traditional clinical outcomes (evaluating the activity of the drug under evaluation in terms of tumour shrinking or disease response) used together with biological measures (evaluating molecular or cellular critical events).

The shared efforts of researchers from both basic and research fields aim to identify (namely, to select) as soon as possible during the Research & Development process potentially effective health interventions (here used in its broadest sense to indicate molecular assays, imaging techniques, drugs and/or biological products) using a combination of pre-clinical and clinical measures. Candidate intervention is then tested further, in a later and confirmative phase of the clinical research (namely, phase III), by comparing the new health intervention with appropriate comparators, such as placebo, best supportive care or well-established active treatments, in terms of safety and efficacy measures to ensure that the benefits of new drugs outweigh their risks [3].

In the USA, ad-hoc funding programs have recently been launched by the NCI to conduct early-stage interventions aimed at establishing the feasibility or the proof of concept of specific translational approaches in several types of cancer http://www.nci.nih.gov/. In Europe, the new VI Framework Program was recently launched to sustain and enhance the collaboration of the European Centres of Excellence in several critical research areas, such as genomics and biotechnology for health http://www.cordis.lu/fp6/eoi-instruments.

The third critical step regards the passage from *clinical research* to *clinical practice*, where the best evidence should be promptly translated into the best medical care. This step should incorporate epidemiology and clinical research, as well as health service research. In the case of drugs, public government agencies, such as the FDA and EMEA, have the specific responsibility of "governing and regulating" this critical step by evaluating the quality, safety and efficacy of new drugs and making beneficial drugs available as quickly as possible. An important role can also be attributed to Evidence Based Medicine (EBM), a movement essentially based on secondary analyses of existing data (either literature or data) which, by using systematic review and meta-analysis, aims to identify which health intervention actually works and should thus be implemented in health care http://www.cochrane.de/cochrane/crgs.htm#CENTRES. As EBM essentially uses data

from clinical research to identify, select, appraise and evaluate the yield of medical interventions, its value and contribution is essentially related to the availability and quality of data made available through the process presented and discussed above.

In addition, the desire to both improve outcomes and control costs determines the need to know how well effective therapies work in the practice setting using indicators that encompass a very broad range of health and non-health domains.

The need to know the actual value of health interventions in health care has led to the re-emergence of Outcome Research (OR), a discipline dealing with research methods and efforts to measure what actually works (effectiveness) in health care using various complementary outcome measures, ranging from traditional clinical measures (symptom control, duration of response, disease progression or survival) to health-related quality of life and cost measures [4,5]. Although there is no consensus on its precise definition, OR is commonly defined as the discipline that describes, interprets, and predicts the impact of various influences, especially interventions, on final endpoints (from survival to satisfaction with care) that matter to decision makers (from patients to society at large) [6].

The role of OR in the (anti-cancer) drug development process

OR is most likely to be successful when it is carried out in a matrix of basic, clinical, and population activities where scientists from several but correlated disciplines work together in pre-planned and integrated projects. In the oncological setting, where historically speaking TR, clinical research and OR are very distinct from each other, they are seen as distinct and separated fields. TR and OR lie at the opposite extremes of a continuum, with little or no chance of interaction and/or cross-fertilization. Clinical research receives input from basic research and alone, or in the context of TR projects, focuses on translating findings derived from basic science to the development of new drugs (with particular interest in research dedicated to obtaining experimental results impacting directly on improving approaches to be eventually tested in later research phases). OR, given its relationship and interaction with health care administrators and/or policy makers, is more interested in evaluating the effectiveness and yield of the application in the clinical practice of alternative therapeutic options made available through the Research & Development process (with particular attention to the use of humanistic and economic outcomes to compare the value of established treatments) [5,6]. OR, seen from the health service research perspective, can be defined as research that focuses on identifying variations in medical procedures *and* associated health outcomes (i.e., evaluation of quality and appropriateness). On the other hand, when seen from the clinical research perspective, the ideal place for OR is between clinical research and clinical practice, in an area usually defined as Phase IV that is supposed to determine the safety and efficacy of health interventions in a broader patient population (i.e., evaluation of effectiveness).

In the latter context, indeed, OR appears to act in different ways, being only apparently integrated into mainstream clinical research. An analysis of the published literature shows more clearly what OR is not (Phase I, II, or III clinical trials evaluating activity, disease progression or survival) rather than what it is [7]. As a matter of fact, although the number of effectiveness studies in oncology incorporating typical OR endpoints (quality of life and cost measures) are increasing, very little evidence is available to answer the question as to whether OR actually affects drugs policy or practice.

The lack of communication and collaboration between basic, clinical and outcome research in oncology is particularly evident in the case of anti-cancer drugs where OR studies are usually carried out by researchers or institutions which are not directly involved in the production of pre-clinical or clinical evidence and are under pressure from policy makers and health administrators concerned about the appropriate delivery of effective health care at the lowest cost. However, there are indications that the present situation could change. Two facts may indeed enhance the role of OR in the field of development and evaluation of anti-cancer drugs.

Firstly, the American National Cancer Institute has launched a new quality-of-care initiative, "The Nation's Investment in Cancer Research" (known informally as the "Bypass Budget") whose goal is to enhance the state of the science for defining, measuring, monitoring, and improving the quality of cancer care, and inform both public- and private-sector decision making on cancer care delivery, coverage, regulation, and standards setting http://plan.cancer.gov/infra/quality.htm. To meet this research challenge, several activities have been planned and budgeted: 1) Define a core set of valid, patient-centred, cancer outcome measures to enhance our ability to compare interventions across studies and over time. 2) Define a core set of process measures to identify those interventions that have been convincingly shown to improve cancer care outcomes. 3) Build a stronger data and methods "infrastructure" for conducting quality of care analyses, including studies to determine which interventions improve patient-valued outcomes. 4) Ensure that therapies shown to be effective in clinical trials are incorporated into community practice. 5) Enhance the quality of cancer communications by gaining a better understanding of the

information needs of patients, families, and other decision makers. It may be noted that some of the above initiatives (1, 2 and 3) are directly based on the principles of OR, while the last 2 are more related to Disease and Outcome Management fields [5].

Secondly, the FDA, recognizing the need for faster drug approval, has recently modified existing regulations and created new rules to allow anti-cancer drugs to be approved more quickly and, in certain but quite common circumstances, single arm trials and surrogate endpoints to be used as measures of clinical benefit http://www.fda.gov/cder/cancer. In this context, there is the possibility that a faster approval process may lead to drugs being marketed which are either ineffective or unsafe. In addition, given the widespread scepticism about the value of patient-reported outcome measures, tumor-response based (TRB) measures have frequently been adopted not only as surrogate endpoints of survival in studies evaluating "curative" treatments but also as surrogate endpoints of better/improved (quality of) life, alone or in combination with ad-hoc composite endpoints (usually referred to as clinical benefit measures) to support and complement TRB findings in "palliative" studies. The move to bring forward an-earlier-than-ideal point along the drug approval path together with the use of surrogate endpoints in a very small sample of patients can be considered either an important step towards ensuring that beneficial drugs are made available as quickly as possible or a dangerous shortcut that might jeopardize the consumers' health as unsafe and ineffective drugs could be marketed and prescribed. On the other hand, it also underscores the need to validate early findings with well-designed studies to verify the true clinical benefit in a broader patient population, thus emphasizing the role of OR. As OR is placed downstream the process of accumulating evidence on activity, safety and efficacy, it is the disciplines that might help understand the value of drugs that have received accelerated approval.

Role of PRO measures in the approval of anti-cancer drugs

Until 1992, marketing approval both in the USA and Europe required substantial evidence as to safety and efficacy, i.e., usually two phase III trials with appropriate clinical benefit endpoints were necessary to demonstrate that the drug either prolonged survival or reduced symptoms. Starting from December 1992 and then in 1996, with the FDA Modernization Act, the FDA changed its philosophy about how much and which information is needed in order to make a decision and also introduced innovations (fast track approach, expedited review and accelerated approval) that both reduced the time for dossier review and made the use of surrogate endpoints possible for most anti-cancer drugs http://www.accessdata.fda.gov/scripts/cder/onctools/Accel.cfm. Although efficacy is still formally considered to be synonymous with clinical benefit and a demonstration of life prolongation or quality of life improvement with well-designed RCTs is formally required, on several occasions surrogate endpoints of quality of life and symptomatic clinical benefit, such as amount and kind of tumour response and non-validated ad-hoc (compound) clinical benefit measures (CBM), and single arm trials have actually been accepted (since 1992, 17% of cases of new anti-cancer drugs used the accelerated approval, 60% using non-survival endpoints and 28% non-controlled and non-masked trials (R. Pazdur, FDA-CDER-DOPD, Personal Communication, 2002)).

The EMEA has less explicit regulations on "quick procedures", and expedited "approval" has been used only in exceptional circumstances (since 1995, only in 2 (10%) anti-cancer drugs [8]), and has thus been criticised for its conservative and rigid position [9]. On the other hand, others have recently raised concerns about the frequent use of non-inferiority and equivalence design in comparative and randomised trials that allows the approval of drugs with much uncertainty as to the merits of the drugs tested [10]. This phenomenon has been particularly evident for anti-cancer drugs. Drugs approved in the first years of the EMEA do not meet the expectations generated by gains in basic knowledge on cancer biology, have not shown significant improvement in survival, safety or quality of life, and cost much more than the standard treatments [11].

Surrogate endpoints based on tumour shrinking indicators are used in therapeutic/curative trials to show the benefits over available therapy as they are considered reasonably likely to predict clinical benefit, namely better survival, and fewer patients and less time are needed to complete a trial. However, the reason why surrogate endpoints of quality of life are used instead of formal (psychometric) quality of life instruments is quite different. Essentially, formal quality of life assessment in clinical trials is considered not only cumbersome, complex and costly but is also plagued by several unresolved methodological and statistical problems that make it difficult to interpret results. In addition, physicians, researchers and regulators are sceptical about the value of such instruments as HR-QoL measures have yet to demonstrate their added value when used together with traditional clinical endpoints [12,13]. A recent and still ongoing evaluation of the added value of HR-QoL measures in published RCTs on advanced breast cancer patients shows that in the retrieved papers very little information was available on important methodological aspects, the tools used were extremely heterogeneous, a large variability in compliance was reported, there was poor correlation be-

tween clinical efficacy and HR-QoL results in most studies, and HR-QoL data rarely contributed to the choice of regimen to be recommended [14].

Hence, although the use of surrogate endpoints and non-validated CBM measures may even be considered a worse option, in palliative settings quality of life data is usually collected but approval is still based on surrogate and non-validated measures [15].

Accordingly, despite the thousands of conceptual and empirical papers published [16] and the genuine recent growth in cultural interest in measuring the relevant qualitative aspects of life most closely related to health and health care- the so called Health Related Quality of Life (HRQOL) [17], regulatory agencies such as the FDA and EMEA do not currently require or recommend the use of this kind of data to approve new drugs. Neither the EMEA nor the FDA have published any guidance document on this issue.

Nevertheless, the two agencies seem to have a slightly different attitude.

The EMEA has included in its recently revised Note for Guidance for anti-cancer drugs explicit statements regarding the use of HR-QoL instruments in phase II-III studies http://www.emea.eu.int. Basically, HR-QoL assessment is accepted and recommended to support tumour shrinking and/or toxicity and symptoms endpoints, justified case per case.

In addition, an assessment of all EMEA recommendations on the use of HRQOL measures in drug approval (recently up-dated by MAPI, Lyon in the context of the ERIQA Project http://www.mapi-research-inst.com) has shown that of the 189 documents retrieved, a few (13/189) contained explicit recommendations regarding the use of HR-QOL measures in regulatory studies, and in most of these (12/13) HRQOL measures were considered as secondary and complementary endpoints [18].

The FDA has neither taken an explicit position nor published any guidance document on these issues. In addition, a comprehensive review of the FDA experience as regards regulatory drug development strategies since 1949 (and the personal opinions of key persons at the Agency) suggests a very sceptical and critical opinion. Although several types of endpoints have served for marketing approval, including objective response rate, time to disease progression, palliation of disease-related symptoms or survival, HRQOL measures have never been prospectively selected as primary endpoints.

Conclusion

PRO and HR-QoL measures have a potential role in the Research & Development of anti-cancer drugs but the field is still plagued by conceptual, methodological and logistical problems. Simpler but not fully validated alternatives (TRB, CBM, etc) are appealing but not appropriate in terms of validity and interpretability. Nevertheless, they are more acceptable to clinicians, researchers and regulators.

The EMEA considers PRO and HR-QoL as a potential efficacy ("symptomatic" clinical benefit) endpoint but it has chosen the approach of not publishing general recommendations that would *prescribe* methodological standards. Nevertheless, there are several guidance documents that explicitly discuss the role of HR-QoL measures.

The FDA is more sceptical. However, a multidisciplinary PRO Working Group, that collaborates with other independent international groups to establish principles and practices for the integration of PRO in the regulatory process, was recently set up and draft guidance documents on HR-QoL will soon be released for comment by the Division of Drug Marketing and Advertisement at the CDER (LB Burke, FDA-CDER-DDMA, Personal Communication).

Pharmas extensively use PRO measures, mostly on cancer products. A recent evaluation and preliminary analysis of the European Public Assessment Report (EPAR) has shown that in at least 25% of the EPAR reports there is a claim about HR-QoL, most (25%) in cancer-related products.

The above facts together with the present move to speed up drug approval together with the use of surrogate endpoints give OR a unique opportunity to demonstrate its ability to verify the true clinical benefit of drugs in a broader patient population using appropriate endpoints, such as PRO measures, and sound design. Although its potential has been documented by a huge amount of literature, OR has yet to demonstrate its role in the specific setting of the research and evaluation of anti-cancer drugs and provide proof of the validity, reliability and added value of its primary endpoint measures when evaluated in a broader context that includes the more traditional (i.e, clinical) benefit measures that are usually considered primary endpoints.

The implementation of lines of OR in the development and evaluation of anti-cancer drugs hinges upon the availability of specific knowledge, methods, instruments and resources and upon their appropriate integration in the mainstream of clinical research. In the USA specific interdisciplinary projects have been launched by the NCI. In

Europe individual areas of expertise and excellence do exist but the problem is twofold. Firstly, collaboration between experts from several fields, such as statistics, epidemiology, psychometrics, economics, decision science, etc needs to be integrated and facilitated. Secondly, appropriate funds need to be made available to implement such efforts and monitor actual results.

The correct placement of OR in the anti-cancer drug development process will guarantee the highest possible standard of validity and reliability of OR at European level and better integration of both translational and outcome research in the mainstream of clinical research on anti-cancer drugs, thus speeding up the introduction of the results of patient-oriented translational clinical research into clinical practice.

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