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Guidelines and Evidence-Based Medicine—Evidence of What?

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ABSTRACT

This paper outlines ways in which evidence has been gathered over past centuries and valid alternative ways in which evidence may still be gathered and applied in clinical and experimental situations in the future without being constrained and limited to randomised trials. Decisions made about the endpoint objectives of randomised studies may be appropriate for some studies but not appropriate for others. This paper argues that evidence based on a logical hypothesis, but not ready or not appropriate for a randomised trial, can still be tested in a controlled study. The value of a new therapeutic regimen for treatment of tumours that have been resistant to multiple lines of systemic chemotherapy can hardly be tested in a randomised trial comparing the new regimen with what has been applied before in the same patient. In such cases of definite response to a new therapy, a patient can serve as his own control. Thus, new ideas can still be tested and new evidence gained but under well-organised, closely observed and safe conditions. The paper argues that under some circumstances such an approach is a legitimate and a more appropriate alternative to the conventional randomised trial approach.

Keywords: evidence-based medicine, guidelines, cancer costs, targeted drugs, progression-free survival, overall survival, randomized studies

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INTRODUCTION

It would be good to think that doctors would always know just what was the right thing to do about every health problem in different people under different circumstances but the reality is that this is not the case. The evidence is not always there for deciding just what is best for each individual patient under different circumstances in which he or she lives.

Guidelines to help decide best treatment in medicine are, and always have been, based on evidence of best treatment that will achieve the desired outcomes. Now, generally referred to as ''evidence-based medicine,'' the principles also apply in determining most appropriate treatments for cancer. The most commonly accepted evidence in recent years is based on statistical analysis of results of randomised chemotherapy treatment programs.[1] In the past, it was assumed that eventually cancers would be cured with drugs like 5-FU, Leucovorin and Methotrexate or combinations of such drugs. However, chemotherapeutic agents alone failed to cure most cancers.

The next question asked by John L. Marshall from Medscape was ''Can cancer be cured by chemotherapy using increasing doses and appropriately integrated new chemotherapeutic agents?''

We are now facing new approaches such as by trying to hit the epidermal growth factor receptor (EGFR) pathway here or hit it there in the belief that it will be close to providing a cure for all or most cancers. By controlling one pathway, we find a few yet uncontrollable pathways in this complicated network of cancer metabolism.[2]

Judging any benefit of combination chemotherapy depends upon what is agreed to be considered an acceptable outcome be it evidence of increased longevity, period of symptom-free health or time before tumour recurrence has developed. Each of these outcomes can be ascertained by computer-based programs, but there is no single program to determine the most desirable outcome for individual patients with different needs, different family and community situations, different financial circumstances, different clinical facilities or different personal wishes. Only most easily measured evidence-based scientific results are integrated into guidelines, but the most desirable endpoint may not have been statistically established?

Professor Benjamin Djulbegovic from H. Lee Mott Cancer Center, University of South Florida, USA, who was a founder and editor of evidence-based oncology, was asked, ''How strong is the evidence-base in oncology?'' He stated that the great irony of contemporary medicine is that despite the tremendous growth of medical knowledge, data on the benefits and risks of available treatment options are often controversial or even non-existent. He had screened more than 12,000 oncology papers published in 108 journals over a 6-month period and found only 1%–2% of the papers reliable enough to confirm best treatment decisions.[3,4] Concerning multiple combinations of chemotherapeutic agents, the pharmaceutical industry pours millions of dollars into sponsoring trials and a great deal of money depends on the results. They are most unlikely to publish results that are not

favourable to the use of their drug. Undoubtedly, the big pharmaceutical industry is under enormous pressure to succeed because every new drug that fails carries a tremendous financial loss. Actually, the pharmaceutical industry contributes the major part in development of new drugs and therapeutic concepts, but in cases of failure, there is considerable financial risk.

Lack of progress and positive results might entail a redefinition of parameters of success and primary endpoints in a study design. While overall survival traditionally was the gold standard in the ranking of new treatment modalities and new drugs, in recent years, progression-free survival (PFS) has taken over that position of primary endpoint in most studies. But how appropriate and useful is PFS as an endpoint? Is it about a long time interval of many months in which patients indeed benefit quality of life because tumour-related complaints occur much later, or is it only a short time span of days, weeks or a few months in which PFS is also affected by the length of surveillance intervals and the accuracy of interpretation of radiographic changes. Modest incremental improvements in PFS might not result in improvements in quality of life or overall survival and indeed in most studies they do not. It is most important that clinically significant improvements in PFS should be accompanied by improvements in quality of life and without undue treatment associated toxic effects.[5,6]

ARE "STATISTICALLY SIGNIFICANT" RESULTS OF TRIALS NECESSARILY ALSO "CLINICALLY RELEVANT?"

Benjamin Djulbegovic's statements from the year 2004 remain valid, and by and large, there have not been essential changes in reporting clinical results. Endpoints of numerous studies were increasingly PFS rather than overall survival time. With very large sample sizes in clinical studies, almost any difference, no matter how meaningless from a clinical standpoint, may be statistically significant. In the FLEX studies (first-line Erbitux in lung cancer), for example, the addition of a new drug, Cetuximab, to the standard therapy with Cisplatin and Vinorelbin in the treatment of non–small-cell lung cancer (NSCLC), a median survival advantage of 2 and 1.2 months, respectively, was revealed. This advantage, however, remained clinically unsatisfactory, especially with regard of the increased costs and increased toxicity.[7]

After evaluating the cost and benefit for elderly patients with NSCLC, Rebecca Woodward and colleagues, from the National Bureau of Economic Researching in Cambridge/Massachusetts, came to the conclusion that only younger patients with operable tumour stages benefit firsthand from better operative techniques rather than old patients who were not amenable to surgery. These elderly and unfit patients are, therefore, treated with chemotherapy.[8] Despite an increase in healthcare spending, life expectancy showed only marginal improvement, increasing an average of 0.6 months, which is 18 days. The expenditure increased by approximately 20,000 US dollars per patient per 18 days added or some 400,000 US dollars per year of life. The authors came to the conclusion that it would be preferable to spend those large amounts of money for smoking prevention and cessation programs. That might perhaps be more rewarding.[8]

The survival advantage in NSCLC was comparably low when Bevacizumab was added to standard chemotherapy schedules. The gain in survival amounted to a median 2.3 months. It was presented as an exciting improvement in survival, whereas, adverse effects like life-threatening or fatal bleeding were also pointed out. The discrepancy between minimal success and exorbitant cost is also seen in the SATURN trial.[9] In this large study, the PFS in the treatment of NSCLC with Erlotinib for maintenance therapy, increased from 11.1 to 12.3 weeks. These are scarcely 8.5 days. Due to the large sample size, the result is statistically significant. However, with regard to the side-effects and the cost, the clinical benefit of an 8 days increase in PFS makes clinical relevance more than questionable. In colorectal cancer, too, skyrocketing costs have been considerable in recent years. Expenses for new agents and regimens have increased 340-fold compared with the old traditional therapies. Whereas the cost for 6 months of systemic chemotherapy with 5-FU/Leucovorin ranged from less than a 100 US dollars, the new combination therapy with Erbitux amounts to more than 50,000 US dollars.

CLINICAL RELEVANCE AND ARISING COSTS

Most cancer therapy is moving in a track of small clinical steps under an increasing financial burden. Clinical evaluations are increasingly targeted to statistical significance rather than realistic clinical progress. It is very questionable whether borderline improvements in PFS of just some 8 to 9 days or even 2 months really have any clinical relevance. They do not justify tremendous expenditures and toxicities. Most progress does not occur with leaps and bounds but with just little steps and paramount expenses. The objective value of the entire process is questionable. The statistical interpretation of such studies also needs critical consideration. An improvement of the 1-year survival rate of pancreatic cancer from 17% to 23% means a 6% increase. Comparing those 6% increase with the 23% 1-year's survival and therefore coming to the conclusion of a 22% improvement in 1-year survival is simply misleading and gives a wrong picture of the realistic clinical situation. In many sponsored studies, a tendency towards biased interpretation of results should not be overlooked. It has been impressive how quickly biological, so-called targeted agents, have been pushed on the market and with such enthusiasm that leading oncologists have often presented them as a ''breakthrough'' in the fight against cancer. Quite often they have suggested visions of a landslide victory against this disease. It has also been misleading how, after recognizing that, in most cases, there was no substantial survival benefit, PFS was taken as a meaningful new endpoint for new studies. In December 2010, the FDA had revoked Bevacizumab for breast cancer—there was no effect in terms of survival time, but many serious side-effects. In this context, we should

again consider Benjamin Djulbegovic's original question: ''Where is the evidence?''[3] and then ''Evidence of what?''

No one can deny that the present methodology of basing new evidence on computer-driven statistics is a valuable addition to gathering new information but they should not become rigid straightjackets; we should not now assume that all evidence achieved in any other way is irrelevant. If they are too strict and inhibit innovations in cancer therapy, in a way, they might become the exact antithesis of most appropriate personalised medicine.[1]

PAST PRACTICES IN GATHERING EVIDENCE

As written by Stephens and Aigner,[10] in former times, often traditional or historically accepted practices just ''grew'' and became accepted without close analysis or criticism. The dominant medical or surgical teacher may have been skilled in practice but unskilled in critical analysis. Each practitioner's own personal experience was often taken as convincing evidence without proper analysis or fair comparison with other evidence or different circumstances. This type of a teacher's belief, or of personal experience in a limited practice, is often referred to as ''anecdotal evidence.'' Although anecdotal evidence may well be true, there is no proof that the outcome seen will be the most consistent when used by different practitioners, in different circumstances and for different patients. To get that ''proof'' practitioners had to rely on the traditional haphazard methods of ''trial and error'' with its inevitable mistakes adding up to ''experience'' and usually no longer the most appropriate method of making progress.[10]

An attempt to more scientifically determine the most likely outcome of different medical practices or treatments has now evolved, especially over last 2 or 3 decades of the 20th century This has been lead by medical scientists and epidemiologists with a statistical frame of mind to initiate "*randomised trials*" as the doctor's basic ''measuring stick'' to evaluate new information. There is still need for solutions based on logic and close and personal relationships between practitioners and their patients. These relationships and evidence gained must not be lost in the momentum for mathematically based science, which, on the other hand, is mandatory once data—like overall survival—in clinical trials are almost identical and the advantage of a defined method can only be determined by means of a randomised study.[10]

When accepted treatment fails to cure or solve major problems associated with cancer or its treatment, the need for testing a concept based on scientific information must not be dismissed but should be tested in a randomised trial if progress is to be made.

THE PLACE OF RANDOMISED TRIALS

Statistically valid well-organised randomised trials are the most convincing method of gathering vital evidence but they can still not be used to cover all situations and all aspects of medical practice. It is important to keep in mind that: ''The absence of evidence'' is not the same as ''Evidence of the absence.'' That is, just because there is no statistical evidence to prove that something is true does not in itself prove that it is untrue. If it is logical, it may be well worth testing if progress is to be made.[10]

Patients with tumours that are resistant and in progression after multiple and repeated courses of systemic chemotherapies cannot be enrolled into randomised trials as, for example, systemic versus regional chemotherapy, because tumours are resistant to systemic chemotherapy and/or patients do not tolerate toxicity any further. In this selection of advanced cases, the heavily pretreated patient can serve as his own control as shown in studies on relapsed and platin-refractory ovarian cancer[11] or NSCLC,[12] both treated successfully with regional induction chemotherapy and chemofiltration.[13]

Finally if, in a ''pilot study,'' a new well-considered treatment program is found to give much better results than any previously known treatment then the morality of subjecting some patients to obviously inferior treatment to satisfy statisticians must be seriously questioned.

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