Conflict of interests, benefits and harms involved in clinical trials in lung cancer

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Abstract

The standard treatment for locally advanced non-small cell lung cancer (NSCLC) is radiochemotherapy (RCT). Unsatisfactory overall survival stimulated initial studies with targeted therapy. This study examined conflicts of interest involved in phase I/II clinical trials using targeted therapy + RQT in patients with NSCLC, based on a previously presented metanalysis. The survival achieved with targeted therapy showed no statistical difference, when compared to standard treatment. However, an increase of toxicities was observed. Besides, 85.7 % of the studies reported conflict of interests. It was found, thus, that the pharmaceutical industry funding is probably associated with favorable results. As shown in the DUBDH, benefits should be maximized and any possible harm, minimized. In this sense, patients with potentially curable disease, undergoing studies (often industry-sponsored), exhibit, though, diminished quality of life. The conclusion of these studies, considered the financial interests of investigators, is often detached from reality.

Keywords: Conflict of interest. Risk assessment. Biomedical research-risk.

Resumo

Conflito de interesses em ensaios clínicos iniciais envolvendo pacientes com neoplasia de pulmão

O tratamento padrão para neoplasia de pulmão de não pequenas células (NPNPC) localmente avançada é radioquimioterapia (RQT). Resultados insatisfatórios de sobrevida estimularam estudos iniciais com drogas-alvo. O presente trabalho analisou conflitos de interesse envolvidos em ensaios clínicos fase I/II utilizando-se terapia-alvo + RQT, em pacientes com NPNPC localmente avançada, com base em metanálise apresentada anteriormente. A sobrevida alcançada não demonstrou diferença estatística, comparada ao tratamento-padrão. No entanto, houve aumento da toxicidade. Além disso, 85,7% dos estudos registraram existência de conflitos de interesses. Avaliou-se que o financiamento, pela indústria farmacêutica, está associado a conclusões favoráveis ao tratamento testado. Conforme a DUBDH, benefícios devem ser maximizados e qualquer dano possível, minimizado. E, no entanto, pacientes com enfermidade potencialmente curável, submetendo-se a estudos frequentemente patrocinados pela indústria, apresentaram qualidade de vida diminuída. A conclusão desses estudos, possivelmente influenciada pelos conflitos de interesses dos pesquisadores, está frequentemente distanciada da realidade.

Palavras-chave: Conflito de interesses. Medição de risco. Pesquisa biomédica-risco.

Resumen

Conflicto de intereses en ensayos clínicos iniciales involucrando pacientes con neoplasia de pulmón

El tratamiento estándar para la neoplasia de pulmón de células no pequeñas (NPNPC) localmente avanzada es la radio quimioterapia (RQT). Resultados de supervivencia, todavía, insatisfactoria, han estimulado estudios iniciales con drogas blanco. El presente estudio ha examinado los conflictos de interés que influyen en ensayos clínicos de fase I/II utilizando la terapia blanco + RQT en pacientes con NPNPC localmente avanzada, basada en meta análisis presentada precedentemente. La supervivencia alcanzada no ha resultado en ninguna diferencia estadística si comparada con el tratamiento estándar. Sin embargo, se ha visto un aumento de la toxicidad. Y además, el 85,7% de los estudios han informado la existencia de conflictos de intereses. Se ve, entonces, que la financiación de la industria farmacéutica puede estar asociada con resultados favorables para el tratamiento probado. De acuerdo con la DUBDH, los beneficios deben ser maximizados y los posibles daños deben ser, minimizados. Y entre tanto, los pacientes con enfermedad potencialmente curable, que se someten a estudios a menudo patrocinados por la industria presentaron una disminución de la calidad de vida. La conclusión de estos estudios, posiblemente influenciada por los conflictos de intereses de los investigadores, se aleja, frecuentemente de la realidad.

Palabras-clave: Conflicto de intereses. Medición de riesgo. Investigación biomédica-riesgo.

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Declaram não haver conflitos de interesse.

Research article

The lung cancer is the most common of all malignancies where men and women are considered together. In 2012 were expected in Brazil 18 new cases per 100,000 men, and 10 for the same amount of women, according to estimates by the National Cancer Institute. A rare disease by the end of the nineteenth century, this neoplasm had its increased incidence in the next century, reaching the figure of 12.7% of all cancer cases worldwide in 2008 (1.61 million new cases provided for that year) [1].

The lung tumors are divided into two main types: small cell cancer (NPC) and non-small cell cancer (NPNPC). The NPNPC is divided into several subtypes of tumors, particularly carcinomas, giant cell carcinomas and squamous cell carcinomas. All of them, until very recently, were treated equally. The NPC are less frequent tumors (approximately 15% of the total), very aggressive from the cellular point of view, and are primarily treated with chemotherapy and sometimes radiation therapy. The NPNPC, in turn, can be divided into initial - when no lymph node involvement or there's only involvement of peribronchial lymph nodes or ipsilateral hilar (stages I and II) - and locally advanced (stage IIIa and IIIb), when there is involvement of lymph nodes ipsilateral mediastinal, subcarinal or contralateral mediastinal. There is also the possibility of evidence of metastatic disease already at the time of initial diagnosis (stage IV). The NPNPC when locally advanced, given the extensive involvement is rarely accessible surgically [2].

The current standard treatment for locally advanced NPNPC is radiotherapy combined with chemotherapy, applied modalities concurrently (RQT) for approximately 45 days. Such approach was defined as standard for meta-analysis published by the biostatistics group of Gustave Roussy Institute, in Paris in 2010 [3]. In this study, the overall survival (OS) of five years among patients receiving concomitant therapy was 15.1% while only 10.6% of patients receiving sequential treatment (one of the modes then the other) were alive at the end of this period. However, despite these strategic advances, and considering the figures presented, the prognosis remains poor, and new therapeutic modalities are urgently needed.

Preclinical data from laboratory studies led to the identification of potential cellular targets that could, in theory, improve the outcome of treatment of lung cancer. Many drugs have been tested since. One strategy is to study the inhibition of the receptor of the epidermal growth factor (EGFR) [4]. Another is the inhibition of angiogenesis in tumor vasculature [5,6]. In both examples, the new drugs - designed specifically to bind to pre-defined targets (target therapy) - are not used alone, but in conjunction with what is known to contribute to the best clinical results currently: a chemoradiation as described previously [3].

Phase I oncology trials are typically designed to evaluate the safety and toxicity of new therapeutic agents [7-9] with unknown toxicity pattern. Such studies, however, when they include the use of radiotherapy, have special features that make them special: first, the maximum tolerated dose of the new drug, when combined with radiation is not necessarily the same as when this drug is used as a single agent alone. Tends to be lower, although this is not the rule. Inadequate control of adverse events (using a dose which is likely exaggerated) may result in the abandonment of a combination due to their high toxicity when such combination would have potential relevance if tested in modest doses [9]. Second, studies that evaluate a single anticancer drug typically recruit patients with advanced disease, refractory to conventional treatments [10]. They are, in general, patients with no therapeutic possibilities, with reduced organic reserves (low resistance to toxicity) and low probability of antitumor response.

On the other hand, the use of radiation therapy trials are generally carried out with curative intention in patients with no previously started treatment and always have, ultimately, the ability to receive the treatment considered standrd, with chances of cure rates and toxicity development widely known [9]. In other words, these studies (phase I with use of radiotherapy) provide information not only regarding security, but also in the therapeutic efficacy, *endpoints* usually evaluated in phase II or III. However, with a smaller group of patients.

In a recent meta-analysis [11], it was observed that, until that moment, if considering all studies from phase I, I/II or II in which there was the use of targeted therapy with RQT in patients with locally advanced NPNPC [12-18], when the results were compared with the standard treatment, patients presented no clinically relevant improvement, as disease-free survival or overall survival. Had, however, statistically significant increase in the level of serious side effects (grade III to V) [19] during treatment - which is quite worrying, since these patients had, at the time of the study, diagnosis of diseases with curative potential.

It is assumed, for the presentation of the following data, that the standard treatment of patients with NPNPC lung cancer is RQT, and that the treat-

ment tested by meta-analysis of components studies is the association of targeted therapy to RQT.

Disease-free survival (DFS) and overall survival (OS)

As shown in Table 1, the meta-analysis demonstrated that disease-free survival in the treatment tested does not differ from what was found in the standard treatment (p > 0.05). Similarly, the median overall survival calculated presents no significant difference from the statistical point of view, between the proposed treatment and the standard treatment. This means that the targeted therapy dos not present, up to the time of disclosure of this study, the advantage over the standard treatment with regard to positive results related to it continuous use. The column named "p*" refers to the level of the test description. The value greater than 0.05 indicates that there is no relationship between the variables studied. In this case, indicates that the use of targeted therapies did not affect the DFS or OS these patients.

Table 1. disease-free survival (DFS) and overall survival (OS) in the treatment tested and in standard therapy.

Survival according to the type of treatment	Survival time of the tested treatment (months)	Survival time of the standard treatment (months)	p*
DFS	**10,0 (7,1-14,3)**	**9,9 (3,1-31,8)**	**p = 0,98**
OS	18,4 (12,9-26,3)	16,2 (14,9-17,7)	p = 0,37

Source: Santos et al., 2012 11.

Toxicity

It was determined the toxicity of the treatment as any sign or negative sign (including laboratory evaluations) occasionally associated with the use of a medication or procedure. Based on the data relating to present serious adverse effects on both types of treatment, tested and standard has been tested showed that treatment 118.5 serious adverse effects, and the standard treatment, 27, during the treatment period, with an incidence adjusted as a function of time (patients 1,000/month). That is, the standard treatment has much less severe adverse effects than treatment tested 11.

Despite such findings regarding survival and toxicity, the findings reported in studies indicated a contrary interpretation, classifying the different approaches as safe and promising. It is understandable that there is commitment of the pharmaceutical industry in the implementation of these studies, with or without the application of radiotherapy, once they involve molecules of considerably high cost. However, given the inconsistency between the results and the conclusions drawn from these, we consider relevant an analysis by the bioethics perspective.

This objective of this work was, therefore, to analyze potential conflicts of interest involved in the conclusions of clinical trials of phase I/II using target drugs and radiochemotherapy (RQT) performed in patients with lung cancer locally advanced non-small cell (NPNPC LA) based on data from previous study 11 evaluating toxicity and the overall survival in these trials reported. We investigated also the correlation between the effectiveness of treatments based on targeted therapy and the participation in the financing and potential influence of the pharmaceutical industry in the conduct of studies in question.

Method

This paper presents the bioethical analysis of meta-analysis results authored by Santos et al. 11, focusing on potential conflicts of interest. The meta-analysis met a total of seven clinical trials of phase I/II conducted in the United States and European countries during the period 2000-2011, using targeted therapy and RQT in patients with locally advanced NPNPC 12-18. The findings presented were then classified by the authors of this study in favorable, unfavorable or neutral on the tested targeted therapy, according to the recommendation (or not) of the use of the drug in later clinical trials or, in daily clinical practice, after the study. Then, these findings were compared with the type of financing (sponsored or not by the pharmaceutical industry) declared in their trials.

Finally, we evaluated issues related to patient selection procedures, the obtention of the informed

consent, benefit and harm to patients. Such discussion was based and had as its main focus the Universal Declaration on Bioethics and Human Rights (DUBDH, acronym in Portuguese) 20.

Results

Based on the results and conclusions presented by the meta-analysis 11, we chose to highlight two points of the study regarding to conflicts of interest and the relationship between issued findings and the source of funding.

Conflict of interests

Upon publication, and as international norms, the components of the meta-analysis studies reported the existence or not of conflicts of interest, indicating the type of financing received (sponsorship or remuneration of the pharmaceutical industry).

From the seven studies that comprise the meta-analysis, four received direct sponsorship of the drug manufacture; in two studies, the authors received remuneration from the drug manufacture, and only one study declared no conflicts of interests, and was sponsored by government agencies. These data show that the universe studied, the vast majority (85.7%) recorded the existence of a conflict of interest.

Findings of the studies according to the source of financing

When the information on the type of conclusion issued by the study is crossed with the funding report or the pharmaceutical industry, it is inferred, from Table 2 that the finance industry is probably associated with favorable conclusions to the studied treatment since most of the sponsored studies showed favorable conclusion and, among all included trials, the only one that was not sponsored by the industry showed unfavorable conclusion.

Table 2. Conclusions issued by the studies (favorable or not the tested treatment) according to the funding source (sponsored / funded or not by the pharmaceutical industry).

Type of conclusion / remuneration or sponsorship	Study sponsored / funded by the pharmaceutical industry	Study not sponsored / funded by the pharmaceutical industry
Successful conclusion	4	0
Mid / negative conclusion	2	1

Source: Santos et al., 2012 [11].

Thus, it is observed by means of the extracted meta-analysis and the results presented here, that the combined use of targeted therapy for the RQT treatment of NPNPC LA, has so far, led to a significant increase in adverse effects, with no change the DFS or OS of these patients. And these studies are often sponsored/funded by the producer of the drug industry. Therefore, such conflicts of interest are likely related to conclusions favorable to the treatments being tested.

Discussion

Regarding the results, we realized that the survival - both global and disease-free - achieved with treatments based on targeted therapy was not different from that of patients who underwent standard treatment. However, when assessing the toxic effects, we can see clear statistical difference, which clearly demonstrates that the innovative treatment did not bring benefits to patients. Instead, there was increased toxicity (including deaths) when the studies analyzed are taken together.

Thus, such lack of benefits for both the research participants as to the possible future users of the test drugs in future trials, compared to the risk degree to which they were and are likely expose other patients is not justified given the current knowledge about these medications. Although the prognosis of patients with locally advanced diagnostic NPNPC is poor, there is still the possibility of 15% cure rate, set by the standard treatment. By accepting to participate in clinical trials with targeted therapy, patients are taking risks and potential damage involved in the test therapy, probably without adequate understanding in this respect.

According to the literature, there is a little understanding, by trial participants, on the purposes of a study with medication under tests. Beauchamp and Childress [21] addressed this issue by presenting informed consent as an important part of the autonomy of research subjects process, highlighting the situation they call “therapeutic misconception”. The authors in question claim that the existence of conflicts of interest is an important factor that limits the understanding of the research subjects. A study

from Steven Joffe et al., from 2001, quoted by Beauchamp and Childress [21], conducted a survey about the quality of information received by participants in clinical trials related to cancer treatment, finding the data below:

- 90% of participants were satisfied with the informed consent process, most of them considering well informed about;
- 75% did not understand that the studies included non-standard treatment and not approved;
- 25% did not know that the primary purpose of the studies which participated was to benefit future patients and that benefits to participants were uncertain.

In relation to studies included in the meta-analysis currently under review, it is important to note that it was not possible to obtain access, through original articles, or even after search in the records of studies, data on patient selection procedures, informed consent, information offered to patients about the type of treatment involved in clinical trials, and their possible risks and/or benefits. However, it is infered here some questions on these issues, since they are sensitive points, in general, in the context of clinical research. This is one of the areas that have been identified as more likely to discussion on ethics and conflicts of interest, especially with regard to the participation of the pharmaceutical industry in the definition, selection processes of patients, conduct, evaluation and disclosure of the results [22]. Commercial interests may end up prevailing over not biased reviews of efficacy, safety and cost-effectiveness [23].

Still according to Beauchamp and Childress, *the informed consent of the processes and the place of autonomy in biomedical ethics are still under development* [24]. It is known that the perception of risk differs between people, especially between research participants and researchers. Thus, the relevant information for decision-making on participating or not in a research, when defined by the researchers, may not be those needed to support its decision. Thus, the necessary autonomy for a patient to decide to participate in a survey should be built by information as broader and detailed as possible, especially those related to the risks and benefits involved, clearly and completely. The patient should be informed, as in the case of the studies in question, that he is giving up a standard treatment, with its cure rate established [21]. Similarly, he should be aware of the risks inherent in the therapeutic test.

In addition to the issue of information, even in possession of all the quality and quantity required, the vulnerability of patients with malignancies and clinical research participants is seen as the ideal limit autonomy for decision making. Such patients are in a situation of vulnerability by the disease, which can put them in a position to accept any alternative that presents itself, given the small chance of existing cure for locally advanced NPNPC (15% in five years). For this reason, it is understood that the acceptable limits of risk to which these patients are diminished may be exposed, and also to be extended to protective measures offered to them.

Still with respect to vulnerability, we should discuss the relationships established between research subjects and researchers. As stated, the patient's vulnerability, imposed by the disease itself, implies relative inability to protect their own interests, making them to deposit all the confidence in the doctor responsible for his care - in general, the same professional who offers to the patient the "opportunity" of joining a research protocol, acting as a recruiter. The dual role of the clinic researcher is pointed out by Beauchamp and Childress as possible generator of conflicting relationships that interfere with the patient's autonomy, relations which can vary between influence, paternalism and dependency [21].

Analyzing situations like this, we can infer that the patient, fully trusting his doctor, does not have knowledge and full understanding that this doctor has other interests by recruiting him to participate on the research. Probably, does not have access to information about the research funding, or on possible links between his doctor - the researcher - and the production of the drug industry test. And even if it was informed of such links, would know the patient, in his vulnerable situation, to assess the implications of these constraints on the study which will participate? Possibly even health professionals have discerniment to assess these implications, which reinforces the perspective of analysis of conflicts of interest as important and necessary.

Beyond the question of autonomy and knowledge available to the patient for his decision making process, Beauchamp and Childress also discuss about the principle of non-maleficence, which requires health professionals involved in the treatment of patients to refrain from causing them any damage. As observed later, the preclinical data available were not safe enough to allow the translation of data for initial clinical studies in humans, which would imply to disrespect this basic bioethical principle. Accord-

ing to the authors, more than *not infringing damage*, researchers must *not infringe high risk of damage* [25] – even facing a disease whose outcome is usually unfavorable, as the locally advanced NPNPC. Probably there was no reasonable level of security, at the time of recruitment of patients, for it.

In complement to Beauchamp and Childress' approach, the bioethical line of thought developed in Latin America, known as "Intervention Bioethics", proposes the use of DUBDH [20] as a *more comprehensive, more democratic* [...] *more concerned with the desires the most vulnerable*, offering therefore a relevant perspective also for the critical evaluation of potential conflicts of interest in the conduct and interpretation of clinical trial results [26]. Particularly in Article 4, DUBDH brings written the following recommendation: *Benefit and harm: The direct and indirect benefits to patients, research subjects and other affected individuals should be maximized, and any possible harm to such individuals should be minimized, when in the case of the implementation and advancement of scientific knowledge, of medical practices and associated technologies* [20]. For dealing of benefit and harm to research subjects, Article 4 of DUBDH has relevance and applicability to the analysis of clinical studies with targeted therapies in the treatment of cancer, given the already discussed vulnerability in patients who are availing themselves to participate in such studies.

Despite the clarity of the situation to the reader, the findings of the clinical trials analyzed point to a completely opposite direction. Of the seven studies, four conclude to the approval suggestion of the drug in the study, claiming to be the proposed treatment "safe and effective". Only one of them indicates the ineffectiveness of targeted therapy and two more studies consider necessary for clarification. By analyzing the discrepancy between results and conclusions, the situation is enlightened. Of the four studies with favorable conclusions to the proposed treatment, all were funded by the pharmaceutical industry. And the only study not sponsored by industry contradicted the continuity of using of the studied drug (Table 2).

Several publications have been discussing and showing the effects of potential conflicts of interest in clinical studies, ranging from biases in the results to the generation of harmful effects to the subjects involved. Such conflicts are pointed out by many authors that, in general, address the conditions under which the professional decision is improperly influenced by interests unrelated to the patient well-being, for example. This classic definition is treated by Thompson, to point out the danger of considering conflicts of interest as just another kind of choice between competing values, which would dilute the nature of conflict and reinforce the idea that they can not finally be avoided [27], a claim which is made by several other authors on the same matter.

Thompson adds that, when it comes to financial conflicts, only one of the interests has presumption of priority. And it is precisely this asymmetry that makes the distinction between conflicts of interest and ethical dilemmas (where both interests have priority presumption). Ethical dilemmas would be involved in issues such as terminality of life, confidentiality or use of humans in researches [27]. In the studies reviewed here, it is clear that financial conflicts impair the assessment of results and the definition of conclusions, generating discrepancy between them. If the test drug caused increased toxicity without proportional improvement in survival, how can one conclude favorably to its use? That situation has no ethical dilemma, but a severe distortion of the scientific method, considering results and conclusions should keep a clear positive relationship. Such distortion is here clearly determined by the financial conflict of interest that is imposed, which may even, depending on the situation, be considered fraud.

Conflicts of interest may also influence the definition of research questions, the study design, data analysis, interpretation of results, the decision on whether to publish the results, and which results to report. Regarding the results, those arising from positive studies and favorable reviews are more likely to be published than unfavorable results for sponsors. Still, compared with studies not funded by industry, the sponsored ones produce, more often, results or conclusions favorable to drug sponsors; exactly as shown by the results reported here. Relations between authors of the studies and drug manufacturers have been linked to direct evaluations favorable to the efficacy and safety of drugs under study [28].

In its report on health policy, Bodenheimer takes conclusions of various studies clearly demonstrating the influence of the pharmaceutical industry in clinical trials with drugs, strengthening the numerous theories about the undesirable conflict of interest [29]. In the same report, Bodenheimer concludes from interviews with actors of the various areas involved in clinical research, that *without the finance of industry, important advances in the prevention and treatment of diseases would not have occurred; but when the results are bad for a particular company, conflicts may surface* [30]. Precisely

considering studies of anticancer drugs, Friedberg and colleagues point out that these present worse outcomes when performed by non-profit research centers (39%) than when performed under the sponsorship of industry (5%) [31].

Other scholars of this subject, while recognizing that the influence of the pharmaceutical industry in various stages of clinical research can be harmful from an ethical point of view, say that when the physician-researcher and his team receive payments from industry, the *value of honorary is a subject that, according to the social pact, is not interest of anyone but the contractors* [32], not shared opinion, given what is discussed above by the authors of this study.

Final considerations

This study sought to explore, as the central problem, the divergence of the results found by initial clinical trials with targeted therapy for patients in treatment of locally advanced RQT NPNPC and its findings, being also analyzed the conflicts of interest reported and its final influence in such studies.

In the field of research related to cancer treatment, it is urgent and important that preventive and therapeutic strategies are developed, and the scientific research on drugs has a fundamental contribution. The question of conflict of interest raised by scholars as crucial, in this subject, is the existence of different goals between the pharmaceutical industry, the cancer treatment centers, the policy makers, researchers and society as a whole, which can result in damage to the integrity and the utility of research [23].

The literature have highlighted the importance of discussing in the context of conflicts of interest, whether it is sufficient to simply be declared a financial interest or if it is the case to admit that the financial interest is a strong potential of bias [23]. In this sense, to declare the existence of conflicts of interest is a necessary step, but not sufficient to mitigate the effects of conflicts of interest in biomedical research [33].

Our understanding points in making the declaration of conflicts of interest compulsory not only in the publication of the studies, as well as the presentation of research protocols to the corresponding ethics committees, and, clearly, also to research subjects. In addition to the statement, it is important to consider the details of the type of the existing conflict, specifying funding amounts and/or remuneration received by researchers and highlighting the possible biases that these conflicts can denote.

Based on the results and conclusions and the internal contradiction between these two stages in the analyzed studies, assesses that the benefit arising to patients is insufficient to justify the use of drugs in tests, and that, moreover, the principle of non-maleficence was little applied, once the toxicity observed in most studies was higher when compared to the standard treatment, with little or no adding justifiable benefit [21]. Even considering that all therapeutic intervention involves some risk of harm, the damage could be justified only if the benefits were greater than the risks involved, which has not been proven true.

To the respect of the autonomy of patients and research subjects implies, in the case of new therapeutic studies, to treat them as ends in themselves, never as mere means. In the perspective the Intervention Bioethics - which, however, is not limited to action on conflict of biomedical nature, nor in the relationship between researchers and research subjects - the recognition of health as quality of life and disease as socially produced reinforces the need to adopt ethical standards that respect human dignity, as also in DUBDH.

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