

## Clinical trials

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## TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Phases of clinical trials
4. Randomization
5. Good clinical practice
6. Clinical trials and cancer molecular biology
7. Conclusion
8. Acknowledgement
9. References

## 1. ABSTRACT

A clinical trial is a research study in human patients aimed at answering specific health questions. If a clinical trial is well-conducted, it is the fastest way to find treatments that work in people and ways to improve health. A clinical trial is one of the final stages of a long research process. It determines whether new experimental treatments or new ways of using known therapies are safe and effective, but it must meet ethical and scientific quality requirements. This paper reviews the principal phases of clinical trials and discusses the basic requirements needed to ensure a well-conducted experimental study.

## 2. INTRODUCTION

A clinical trial is a scientific experiment performed in order to evaluate one or more treatments in a specific population of patients. There are different types of clinical trials. Treatment trials are conducted to test new treatments or new combinations of drugs. They can also test new approaches to surgery or radiation therapy. Prevention trials attempt to prevent disease in people with no previous history of the disease, or to prevent a disease from returning. There are also diagnostic trials, conducted to find better tests or procedures for diagnosing a particular disease or condition, and screening trials, aimed at

## Clinical trials and anti-cancer therapy

identifying the best way to detect specific diseases or health conditions. Finally, quality-of-life trials (or supportive care trials) explore ways to improve the quality of life for individuals with a chronic illness.

### 3. PHASES OF CLINICAL TRIALS

Clinical trials are usually conducted in a series of steps, called phases. During the first step, the phase I trial, researchers test a new therapeutic approach in humans, to evaluate what dose of a new drug is safe, how it should be administered and how often. The primary objective is to determine the maximum tolerated dose. Therefore, during this phase, clinicians define the most frequent side effects and toxicities of the treatment, by treating their patients with increasing doses. During phase I, it is also possible to study the pharmacokinetics of the evaluated drug. It is probably better to select patients with good performance status, when possible, since a poor performance status could cause toxicities even in patients treated with low doses, and this would provide erroneous data.

The second step is the phase II trial, whose objective is to study the therapeutic index of a new drug, its safety and effectiveness. Usually during this phase, patients with measurable disease are selected, in order to evaluate in a short time if the disease is responsive to the studied treatment. In addition, the number of patients is limited and the study focuses on a particular type of disease. The dose of the administered drug is established in the phase I trial (1-3). The most important objective of phase II studies is to prevent inactive drugs from being used in clinical practice. During this phase, the effectiveness of the studied treatment is relative to the dose and the method of drug administration used in the study, as defined in the clinical protocol. Therefore, phase II studies do not provide information about different drug doses and different methods of administration.

After phase II, the new drug is examined in a phase III trial, in which its effectiveness is compared with the standard therapy for the studied disease. Usually, the first objective in this phase is to determine if the new treatment is more effective than the standard one, but there are phase III trials that also investigate if a more conservative treatment could obtain the same results as a standard therapeutic approach. To date, in cancer research, after phase II trials, the new drug is given to patients in combination with other agents, to increase its effectiveness. A phase III trial could be also defined as an experimental study in which different schedules of chemotherapeutic agents are compared.

Patients are randomly assigned to the standard group or the experimental group, usually by computer. This method is called randomization and it helps to avoid bias and ensure that human choice or other factors do not affect the study's results.

A variety of phase III trials have demonstrated the activity of numerous new drugs, alone or in combination with other compounds.

For example numerous phase III trials have been conducted to investigate the benefit of adding taxanes to anthracyclines in first-line chemotherapy for metastatic breast cancer. A meta-analysis of all these studies shows that the adjunction of taxanes to anthracyclines determines a significant benefit in activity and a trend in Overall Survival, although the combination therapy has a more hematological toxicity than the treatment with anthracyclines alone (4-7). Phase III trials have also shown the clinical activity in non-small cell lung cancer of pemetrexed (ALIMTA, LY231514, MTA), a novel antimetabolite that inhibits at least three enzymes involved in the folate pathway. In non-small cell lung cancer, single-agent activity has been documented in the first- and second-line and promising activity has also been demonstrated when pemetrexed is combined with platinum compounds, vinorelbine, and gemcitabine (8-12). Phase IV trials are conducted to further evaluate the long-term safety and effectiveness of a treatment. They usually take place after the treatment has been approved for standard use. Several hundred to several thousand people may take part in a phase IV study. These studies are less common than phase I, II, or III trials.

### 4. RANDOMIZATION

The primary objective of a clinical trial is to obtain results without the influence of factors that are not relative to the study. In order to do this, it is better to choose a group of patients that is as homogeneous as possible. Randomization is a method by which it is possible to eliminate potential unknown factors, which may be able to change the results within the studied population of patients. Through randomization, patients are assigned to groups that are the same overall, and so any different results in the study would be due to the treatments. Randomization is an essential condition for a good statistical evaluation of the study. However, randomization could also present some problems. Physicians must indicate to the patients that they do not know which is the best treatment, the new treatment or the standard one; they are likely to be more interested in a new experimental approach. The group of controls might be considered uninteresting for research, since the results of the treatment are already known. With randomization the different treatments studied can be compared objectively. At the time of the trial, it is not known which treatment is the best; therefore, the patient must choose whether or not to participate in a randomized trial. In fact, an essential condition is that the patient is well-informed about the study. The informed consent is a document, which is very important for medical-legal purposes, confirming the patient's decision, written, dated and signed, to take part in a clinical trial. This decision must be made by the patient freely after being duly informed about the nature and significance of the trial, its implications and risks. However, signing the form does not force an individual to remain in the study. An individual can leave the study at any time, either before the study starts or at any time during the study or the follow-up period. If new benefits, risks or side effects are discovered during the study, the researcher must inform the patients and they may sign new consent forms if they decide to stay in the study.

## Clinical trials and anti-cancer therapy

An important clinical randomized trial is the ATAC study. The 'Arimidex', Tamoxifen, Alone or in Combination (ATAC) trial is an example of a randomized, double-blind trial. It compares anastrozole ('Arimidex'), alone or in combination with tamoxifen, relative to tamoxifen alone as 5 year adjuvant treatment for postmenopausal women with early breast cancer. After 5 years of follow up the study has shown that the third-generation aromatase inhibitor Anastrozole should be the preferred initial treatment for postmenopausal women with localized hormone-receptor-positive breast cancer. This is a clear example that shows how a well conducted clinical trial could change the standard approach to treatment of a disease. Tamoxifen is currently considered the best endocrine option available for adjuvant therapy, but this study demonstrates that effective and better-tolerated endocrine alternatives for early breast cancer treatment are available (13-15).

### 5. GOOD CLINICAL PRACTICE

It is also necessary to make provisions for the monitoring of adverse reactions occurring in clinical trials using Community Surveillance (pharmacovigilance) procedures. This ensures the immediate termination of any clinical trial in which there is an unacceptable level of risk. The accepted basis for the conduct of clinical trials in humans is founded upon the protection of human rights and the dignity of the human being with regard to the application of biology and medicine, as for instance reflected in the 1996 version of the Helsinki Declaration. Good clinical practice is a set of internationally recognized ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. Compliance with this good practice provides assurance that the rights, safety and wellbeing of trial subjects are protected, and that the results of the clinical trials are credible. A clinical trial may be initiated only if it is approved by the Ethics Committee and/or the competent authority. The ethics committee is an independent body consisting of healthcare professionals and nonmedical members, who have the responsibility to protect the rights, safety and wellbeing of human subjects involved in a trial. The Ethics Committee must come to the conclusion that the anticipated therapeutic and public health benefits justify the risks. A clinical trial may be continued only if compliance with this requirement is permanently monitored. To verify this compliance, inspectors are appointed to inspect the trial sites, the manufacturing site of the investigational product and any laboratory used for analyses in the clinical trial. Once a new approach has been proven safe and effective in a clinical trial, it may become standard practice (Official Journal of the European Communities, Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001).

### 6. CLINICAL TRIALS AND CANCER MOLECULAR BIOLOGY

In cancer treatment clinical trials are very important instruments in order to find new effective therapies. Standard treatments for cancer patients include chemotherapy, that, however, is toxic, non specific, and inaccessible to those with a poor performance status.

Alternatively, new treatment options that involve inhibiting specific molecular targets are emerging in the field of experimental therapeutics.

Over the last few years, new molecular markers have been discovered as important targets for diagnosis and therapy. One goal is to identify a specific molecular assay for each tumor and then to obtain an individualized therapeutic approach. By now, in a variety of clinical trials the activity of new molecular agents that acts against molecular targets is being studied. The presence of a molecular target in malignant cells can determine a more specific effect of the therapy and can cause a reduction of the toxicity. In this paragraph we are going to discuss the role in clinical care of some of the new molecular agents discovered over the last few years. One pathway that has been investigated is that of the epidermal growth factor receptor (EGFR), and its associated tyrosine kinase domain. The EGFR is overexpressed by a wide variety of epithelial neoplasms, including head and neck cancers, breast cancer, colon cancer, and renal cell carcinoma, among others. High expression generally is associated with chemotherapy and hormone-therapy resistance and poor outcome. Targeting the EGFR receptor and/or its associated kinase may be considered a novel therapeutic strategy in cancer therapeutics. Monoclonal antibodies (mAb) are one of a variety of approaches that have been developed to block EGFR activation and they have been shown to be effective against different kinds of cancer (16). For example, in colon cancer patients phase I and II clinical trials have demonstrated that the toxicity of these agents is well moderate and that they are active in patients with advanced disease. EGFR monoclonal antibodies have demonstrated to be able to increase the response rate to therapy, time to progression and overall survival in metastatic colon cancer patients. Therefore, they increase the effects of chemotherapy with standard agents. Cetuximab, ABX-EGF, EMD 72000 are mAb against EGFR currently being evaluated in clinical trials in patients with colon cancer (17-19). A randomized, multicenter, phase II study has shown that cetuximab improves response and survival rate also in patients with Non Small Cell Lung Cancer (NSCLC) receiving Cisplatin plus Vinorelbine as first line treatment, without aggravating chemotherapy toxicities (20).

OSI-774 (Erlotinib) is a recently developed small molecule that results in inhibition of the downstream components of the EGFR pathway. A phase I trial of OSI-774 in patients with solid tumors has shown that it is active in inhibiting the growth of different EGFR-expressing cancer at minimal concentrations. Studies in healthy human volunteers have demonstrated that single doses could be administered with only moderate toxicity (16). To date, OSI-774 and ZD1839 (Gefitinib) are the most studied of the EGFR TKIs for the treatment of NSCLC. Approximately 85% of all lung cancers are categorized as NSCLC, which expresses EGFR at a rate of 40%-85%. Three recently completed trials are investigating the activity of Erlotinib as monotherapy (BR.21 study) or in combination with standard chemotherapeutic regimens (TALENT and TRIBUTE trials) for the treatment of

## Clinical trials and anti-cancer therapy

NSCLC. When used in combination with carboplatin/paclitaxel (TALENT) or cisplatin/gemcitabine (TRIBUTE), erlotinib was not found to improve survival, but it has exhibited overall survival benefits when used as monotherapy (BR.21 study) (21).

Phase I and II studies have demonstrated that ZD1839 is active in colon, ovary, breast, prostatic, NSCLC, head and neck and kidney cancers (22). ZD1839 and OSI774 are currently evaluated in phase I and II trials in head and neck cancer patients and first results show that they increase the activity of chemotherapy and radiotherapy (23-25). Clinical trials with ZD1839 in combination with anastrozole, trastuzumab, fulvestrant and chemotherapy in breast cancer patients are ongoing (26). In lung cancer also cyclooxygenase (COX)-2, an enzyme involved in prostaglandin production in pathologic states, is often overexpressed in premalignant and malignant lesions and preclinical studies suggest that COX-2 may be involved in the molecular pathogenesis of some types of lung cancer. Phase I and II clinical trials of the combination of selective COX-2 inhibitors with radiotherapy, chemotherapy, or both in patients with lung cancer have been initiated. Celecoxib, a selective COX-2 inhibitor, seems to increase the antitumor effects of chemotherapy in patients with NSCLC (27, 28). Clinical trials currently underway are exploring the potential of targeting histone deacetylases (HDACs) in the treatment of cancer. The histone deacetylase inhibitors (HDIs) are a new class of antineoplastic agents currently being evaluated in clinical trials.

Gene expression may be modulated by post-translational modifications, such as acetylation, phosphorylation, methylation and ubiquitination, that alter chromatin structure. Two groups of enzymes, HDACs and acetyl transferases, determine the acetylation status of histones (29-32). Inhibitors of HDACs activity have been shown to be active in vitro and in vivo in causing cancer cell growth arrest, differentiation and/or apoptosis. Several structural classes of compounds have been shown to exert histone deacetylase inhibition, including sodium n-butyrate, suberoylanilide hydroxamic acid, LAQ824, CI-994, MS-275, and depsipeptide. HDAC inhibitors are currently in clinical trials as anticancer agents and preliminary results suggest that these agents are very promising (33, 34). In particular, hydroxamic acid-based HDIs have shown activity against cancers at well-tolerated doses and dramatic responses have recently been observed in patients with T-cell lymphomas treated with depsipeptide, one of the newer agents (35, 36). New evidences show that HDIs may act also through mechanisms other than induction of histone acetylation and it is conceivable that the final activity of HDIs in cancer therapy is to act as modulators of apoptosis induced by other cytotoxic agents (33).

Recent studies have shown that also the proteasome is a valid target for anti-cancer therapy. Several tumor suppressors, transcription factors and oncogenes are degraded by the proteasome pathway. The inhibition of this pathway affects the levels of various short-lived proteins and results in inhibition of NF- $\kappa$ B activity, increased activity of p53 and Bax proteins and accumulation of cell cycle

inhibitors p27 and p21. PS-341 (bortezomib) is a boronic acid dipeptide and it is a specific inhibitor of proteasome pathway. Several clinical trials are currently ongoing with bortezomib in hematologic and non-hematologic malignancies, alone and in combination with other active agents. The Food and Drug Administration has approved PS-341 as an anti-myeloma agent. It is the first proteasome inhibitor to enter clinical practice and it has validated the proteasome as a new valid target in cancer therapy (37-40).

## 7. CONCLUSION

Clinical trials expose the physician to some problems, such as possible conflicts between the role of the clinician and that of the researcher. If the clinical researcher is convinced that one treatment is better than another in a clinical trial, he/she tends to administer the treatment believed to be the best, while the researcher must aim to conduct a study that is the most scientifically correct. Furthermore, it is important that a scientific study be conducted with the best interests of the patient in mind, without being influenced by the pharmaceutical companies.

A randomized trial must meet some basic requirements, even if results may produce only confusion and other questions. The basic requirements are: a clearly defined objective, important clinical questions, a suitable number of patients and precise statistical analyses.

If a clinical trial is not well-conducted, patients may be deprived of better available treatments. On the other hand, when conducted properly, clinical trials it is the fastest way to find treatments that work in people and ways to improve health.

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