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Clinical trials on oncology studies- a review

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Abstract

Clinical trials plays major role in making the drug safety and effective for the patients suffering from diseases. Cancer disease is one of the leading causes of deaths. Oncology clinical trials are very crucial for the patients, as this might be the only hope for the survival. However, eligibility criteria decides the patients participating in the trial and all the patients should be screened molecularly. There are certain barriers that shut out the patients from enrolling in the clinical trials. Age, gender, race, family status, literacy also affects the patient's participation into the trials. Of all the population participating in clinical trials, elderly population represents almost 25-30%. There are different phases in the clinical trials like Phase 1, Phase 2, Phase 3 and Phase 4 with different criteria and different endpoints. Phase 1 aims on safety, phase 2 aims on efficacy, phase 3 aims on the therapeutic effect of drug, whereas phase 4 deals with the long-term effects of the drug in the market.

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Introduction

Clinical trials are pivotal for the treatment of cancer, and information on the present level of oncology research is required to establish benchmarks and provide the groundwork for future advancements [1]. Oncology Clinical Trials are essential for establishing the evidence to make treatment decisions and to determine the direction of future clinical trials. The standard of patient care can be set by various factors like, evaluating the safety and efficacy of new therapies, and comparing the efficiency of existing therapies [2]. Oncology is more complicated than other clinical trials because the endpoints differ greatly. One of the main differentiators is comparator drugs. Placebos are never used when there is an existing drug [3]. Cancer treatment is becoming increasingly expensive. However, due to a number of factors, such as the paucity of comparative effectiveness research, inefficiencies in trial execution, rising use of off-label medications and growing dependence on less reliable trial designs, our understanding of the value of the care being provided has not kept up. The reorganisation of the cancer cooperative groups, the introduction of patient-centred outcomes, and the development of research criteria such as success in accrual of targeted study sample size are the concerns about clinical research. To our knowledge, however, the information required to fully comprehend the characteristics of oncology trials now being done and their capacity to improve clinical treatment is still lacking [1].

The science of oncology clinical trials evolved to include

Phase I – dose-finding studies

- Phase II - establishment of efficacy in a single tumor type
- Phase III - comparing standards of care with potential advances in care Phase IV – extending safety and data activity in post-marketing.

As a result, we can expect higher cure rates [4].

Reasons for accepting or declining trial entry

Eligibility criteria are the main components of clinical trials. The primary purpose of eligibility criteria is to protect the safety of the patients that participate in the trial and to define the characteristics of the study population [5]. Although elderly patients represent approximately two thirds of cancer patients, they account for only 25% to 30% of clinical trial participants [6]. Elderly minorities, theoretically subject to the combined barriers to participation that characterize elderly and minority communities, may have the greatest risk of low trial participation.

Barriers for acceptance

There are certain factors like mistrust on research and the system, fear, culture, family considerations, transportation, low health literacy that act as barriers for the patients to participate or to accept the trial. Some other barriers are language, where the native language enhanced the communication. And the other barriers include comorbid conditions, inadequate health insurance [7].

Challenges and opportunities

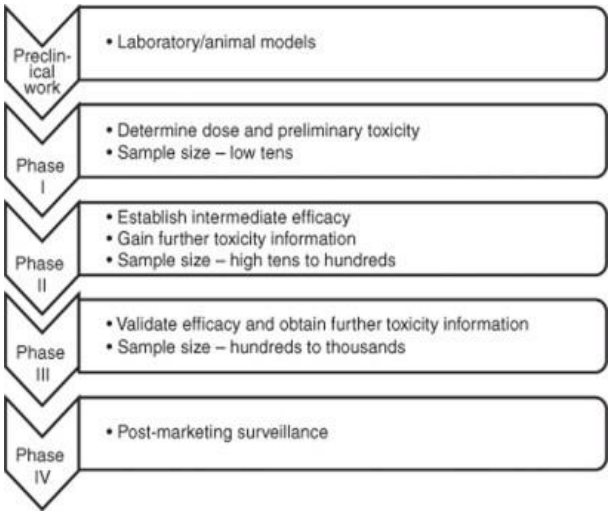
Oncology is multidisciplinary in nature. Nonetheless, clinical trial designs that functionally evaluate multimodality regimens past simple combination remain troublesome because of various challenges including appropriate controls and blinding. Trial designs that consolidate modern biomarkers furthermore, assess different treatment modalities in various combinations and sequencing with regards to targeted treatment remain an unmet need.

Current and future clinical studies require a vigorous and dedicated framework for which large health care centres are appropriate. Although the treatment of patients inside their communities offers accommodation and profound relationships supported by geography and communities is where most of the cancer care is delivered [8].

Evaluation of new cancer therapies

The clinical assessment of new cancer treatments, whether new medications or biological approaches, has two objectives: 1) to define safety and 2) efficacy. Generally these objectives have been met through several phases of clinical trial that determine the optimum dose, pharmacokinetics, toxicity and the activity of new medication as estimated by its ability to instigate cancer relapse and develop survival or quality of life [9].

Phases of clinical trials in oncology



Phase 1

The objectives of phase 1 trials are to define the safety, tolerability, maximum tolerable dose of a novel drug by enrolling patients with wide variety of advanced cancers that are resistant to traditional therapy. New methods for dose escalation, patient selection, and research objectives are being included into ongoing phase I studies as a result of the introduction of MTAs (Molecularly Targeted Agents).

Dose Escalation

The traditional 3 + 3 design is a straightforward algorithmic strategy that uses a set of guidelines for dosage escalation that are predetermined and are based on the observed rate of dose-limiting toxicities (DLTs) within a certain assessment window, usually 28 to 30 days. The recommended phase II dose (RP2D) for further research is typically the MTD, which is defined as the dose level at which the DLT rate is less than 33%. This design is best suited for cytotoxic drugs which are known for having positive correlation between dose, efficacy and toxicity and the highest dose with acceptable toxicity is expected.

Patient selection

It is currently understood that most cancers are result from a number of somatically altered oncogenes, each of which contributes a small effect and accumulates during tumour formation, rather than a single dominant gene. As a result, even within the same cancer type, different sets of genes and pathways are responsible for different types of tumours. It is the heterogeneity that underlies the observed varied responses to MTAs. Patients should be screened molecularly to determine their eligibility criteria. Molecularly characterised subgroups of patients are innately small. Only 5-20% of patients who have enrolled for clinical trials were eligible for targeted therapy. This high attenuation is a concern, in any case for non- eligible patients yet in addition as to time and funds. Subgroup analysis for an endurance benefit in heterogeneous populaces expect to identify groups of patients for other treatments in precision medicine. Subgroup analysis relies upon the relation between the drug and the target [10]. When the prevalence of the relevant biomarker is low, a large number of patients must be screened in order to identify a few potential candidates, and additional studies must be launched at single centre in order to accommodate all patients who wish to enrol in a trial. Moreover, since numerous biomarkers are disease specific, centres should be able to huge number of patients for disease specific expansion cohorts which might impose a challenge when phase 1 isn't very much coordinated with subspecialty clinics. Methodologies that facilitate the inclusion of molecularly selected patients are required, like molecular pre-screening programs for metastatic patients to ease the transition to phase 1 trial on the progression of disease.

Endpoints

The standard primary endpoint of phase 1 trial has been toxicity with efficacy as only an optional outcome. Be that as it may, with the new advanced treatment assignment made by the U.S. Food and Drug Administration (FDA) to expedite drug development, getting early evidence of efficacy is currently an important component of phase 1 trials. This has expanded the use of tumour-specific expansion cohorts to further characterize both wellbeing and clinical response at the RP2D, which is related to the higher success rate of phase 2 trials and rapid drug approval. As mentioned above, the organisation of some phase 1 centres also has been rebuilt around disease specific investigators and clinics [11].

Phase 2

The phase II clinical trial plays a major role in drug development in oncology. After phase 1 trial determines the tolerable dose for a new drug, properly designed phase 2 trial should bring forth the information needed to proceed regarding subsequent phase 3 testing. As phase 3 trials require many years, hundreds or thousands of patients and huge amount of money, the data that a quality phase 2 trial can provide is important and is essential to take a decision regarding investment in large trial.

Need for phase 2 trials

Phase 2 trials are the proof of concept trials, used for determining whether particular drug or combinational drug should be studied further. In this regard they serve as an important filtering mechanism in which the negative trial should lead to cessation of new drug development for selected indication. Improving the filtering process is the critical issue: too compact filter will put an end to promising agent improperly, but a too permeable filter will bring about an inordinate number of expensive negative phase 3 trials. In the previous era of oncology drug development, there were not very many medications accessible for the study, and as such a permeable filter was exceptionally proper to limit the likelihood that a false negative outcome would result in the disposing of a promising agent. In the current era, there are many investigational oncology drugs accessible for the study. Accordingly we accept that it is more suitable to use a more compact filter, one that only advances to phase 3 development of those agents for which there is likelihood of success in phase 3 trials is high.

Randomisation in phase 2

Randomisation is underutilised in early clinical studies in oncology. The utilization of randomised trials permits total flexibility in the decision of endpoints, especially if blinding can be incorporated. This method is most powerful and reliable technique for differentiating the effect of drug from a placebo, a fundamental predicate for a effective phase 3 trial. Given that a large number of agents are now available for clinical studies, the expenses of phase 3 trials and limited patient and monetary assets, available for such testing, the expanded use of randomised phase 2 trials gives a reasonable way to move new agents ahead [12].

Phase 3

Phase 3 clinical trials are viewed as gold standard to demonstrate the impact of an experimental treatment compared to standard treatment for the disease of interest. For example, new drugs must typically be shown to have an adequate degree of safety and efficacy in two independent phase 3 trials before they are endorsed for marketing by health authorities. Similarly, new therapies are adopted in clinical practice if they have been tested in no less than one well designed and one well conducted phase 3 clinical trial [13].

Positive and Negative trials

To be classified as positive trial, trial outcome must have achieved a statistically significant finding in favour of the new, experimental treatment for an assigned essential endpoint as per the statistical design pre specified in the protocol. A trial with a negative outcome demonstrated there was statistically significant finding in favour of standard therapy. A trial with null outcome showed that there was no statistically significant advantage for either experimental or standard treatment [14].

Significance of Phase 3 trials

Phase 3 trials are the ideal way to find a new standard for treatment. When a phase 3 study is completed, the groups of patients can be directly compared to each other to evaluate results. (In other words, researchers can check whether one group showed improvement than the other.) If patients on the new therapy improved, a new standard of care may be established. Therefore, this kind of trial might bring about drugs gaining approval and changing the doctors treat patients. Promising treatments might arise in different phases, but those trials are not enough to change standards of care or the manner in which we treat patients.

Phase 4

Phase 4 trials aim is to find out:

- More about the safety and side effects of the drug
- Long term risks and benefits
- How well the drug works when it is used more widely

Drugs which are approved by FDA are watched over for a significant period of time in phase 4 trials. Even after subsequent testing a new drug on thousands of people every effect of the drug may not be known. Some queries are still need to be answered. For instance, a drug might get approval from FDA since it was shown to decrease the risk of cancer recurring after treatment. However, does this imply that the people who get are more likely to live longer? Are there any side effects that haven't been seen yet? Or the side effects that only appear after an individual has taken the medication for long time. These sorts of questions might require and many years to answer and are many times addressed in phase 4 trials.

Important points about phase 4 clinical trials

- Phase 4 studies concentrate on the drugs that are previously approved by FDA. The drugs are accessible for doctors to prescribe to patients, however phase IV trials may still be expected to address significant inquiries.
- These studies may involve thousands of people
- These are the safest type of clinical trials, in light of fact that the treatment has already been studied and has likely been given to many patients.
- Phase 4 studies put more concentration on safety over time.
- These studies may likewise look at other aspects of treatment as well. For example quality of life and cost effectiveness.15

Conclusion

Oncology clinical trials play a major role in improving the safety and the life expectancy of cancer patients. Of all age groups, elderly patients are less enrolled in the study when compared to other age groups. The reasons for the acceptance and declining from the clinical trials are ruled out. The objectives of phase 1 trials are to define the safety, tolerability, maximum tolerable dose of a novel drug. Dose escalation, patient selection, and research objectives are included to improve the phase 1 outcomes. These helps in knowing the MTD. Phase 2 is to know the efficacy of the new drug, it may also involve randomization. Phase 3 includes the testing of the novel drug against the standard drug to know the capability of the experimental drug. Phase 4 involves vast range of people of various backgrounds, history, medical history from which safety of the pre-approved drug is determined.

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