Rational Clinical Trial Design in Cutaneous Lymphoma

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Introduction

In a perfect world almost all medical treatment decisions would be based on statistically significant data collected in randomized clinical trials. Well-defined assessment methods and endpoints are needed in order to compare new drugs with data and endpoints that are collected in a uniform manner. Sharing of data across international boundaries would also help to ensure that new drugs would become more freely available without local restrictions. In addition, with the sequencing of the human genome completed, it should be possible to determine in advance whether a patient will respond to an agent before its administration. In the absence of clinical trials, the use of a drug for an off-label orphan indication should be encouraged and reimbursed, regardless of whether there is a labeled indication. This article will review steps for new drug approval in the United States at this time, and discuss a rational approach and future directions to the conduct of clinical trials for cutaneous T-cell lymphoma (CTCL).

Drug Development

In the United States there is a required pathway for developing a drug for use in humans. Before entering a clinic, evidence of the effect of this drug is collected in preclinical experiments in cell lines, ex vivo tumors, and xenograft models where feasible. High-output screening of drugs can incorporate biologic activity in the selection process. If a drug is of interest, toxicity studies must first be performed in animals and bacteria before minimal dose toxicity in humans can be estimated. Normal human volunteer studies are then performed to study drug pharmacokinetics and clearance before clinical efficacy studies. A new drug application (investigational new drug [IND]) is then filed by the investigator to the US Food and Drug Administration (FDA), and a series of clinical studies and discussions precedes drug approval for use in human subjects under the package insert. An intelligent clinical trial design is critical in order to get statistically meaningful information supporting the IND.

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Types of Clinical Trials

Pilot Studies. Pilot studies are helpful when there is no information about the response rate of a drug in a disease where there could be a biologic effect. Pilot studies enroll only a small number of patients, usually 10-20, who are not randomized, and are descriptive in nature. They are often investigator initiated. Their small size precludes randomization or use of a placebo arm, though it may be possible to use a vehicle control in topical half-body design. Pilot studies are also used to assess the preliminary efficacy of an approved drug, when used for another indication. Pilot studies can also be used as the front end of a stage I/II trial in a 2-tier Simon design.[1]

Phase I and I/II Clinical Trials. The primary goal of all phase I trials is to determine drug toxicity and safety, and to identify the maximum tolerated dose (MTD) of a new drug. The most common design is a dose escalation with cohorts of 3 patients sequentially enrolled at increasing doses. Generally, the first dose selected is well below the toxicity seen in preclinical animal studies. If an adverse event occurs that is thought to be related to the drug, the cohort of 3 is usually expanded to 6 patients to see if the event reoccurs. Examples of CTCL phase I and II clinical trials are shown in Table 1.[2-5]

When a dose-limiting toxicity (DLT) appears, the MTD is the dose level below it and is used to study a larger final cohort, for example a phase II Simon design.[1] Phase II trials are used to determine an optimal dose that is safe and identify a preliminary response rate. The Simon design has an interim analysis built into it after a predetermined number of patients have been treated. If there is insufficient evidence of efficacy, the trial is terminated for reasons of futility. This approach prevents patients from being exposed to ineffective agents and saving time and expense. The time for the interim analysis (generally after 12-15 patients have enrolled and reached a certain time point) will depend upon the estimated response rate that also determines the final numbers of patients to be enrolled. Phase II trials require much smaller numbers of patients than phase III trials.

Two phase II 1-arm clinical trials conducted with similar findings were accepted by the FDA for both registration of bexarotene

Table 1 List of Examples of Phase I and II Clinical Trials for Cutaneous T-Cell Lymphoma

- Phase I trial of bexarotene gel 0.01%, 0.05%, and 0.1%, increasing strength and number of applications; this was followed by a placebo-controlled phase III study and FDA approval[3]
- Vorinostat phase I oral and intravenous dose range including all types of malignancies and identified activity in CTCL[4]
- Vorinostat dose-ranging study found 400 mg dose for phase II Simon design[2]
- Pralatrexate, descending dosing cohorts[5]

Abbreviations: CTCL = cutaneous T-cell lymphoma; FDA = Food and Drug Administration

Table 2 List of Phase III Trials for Cutaneous T-Cell Lymphoma

- Sequential skin-directed therapies versus aggressive chemotherapy showed no difference in overall survival; the study took 10 years to accrue patients at the NCI[9]
- Denileukin diftitox: 2 dose arms for CTCL patients receiving ≤ 3 previous therapies[10]
- Denileukin diftitox versus placebo control in CTCL patients with < 3 previous therapies; found that 18 µg/mL and 9 µg/mL are better than placebo for RR and progression; > 10 years to accrue, 47 patients per arm, crossover possible

Abbreviations: CTCL = cutaneous T-cell lymphoma; NCI = National Cancer Institute; RR = response rate

(early- and late-stage patients)[6,7] and vorinostat for CTCL.[2,8] Phase II randomized trials are built on the assumption that there exist 2 equal populations of patients, 1 of whom with received treatment, and the other who will receive either no treatment (placebo) or standard of care. They assume that treatment will affect either survival, response rate, or be safer or less expensive. The future randomized trial for FDA approval will compare the old drug versus the new drug head-to-head, or a combination of old drug plus new drug versus the old drug as monotherapy. This has been called the beat them or join them approach to drug development (Owen O'Connor, personal communication). If a new active drug is to be compared with a placebo, the trial may contain a crossover design whereby patients who are randomized to placebo receive active drugs if they progress or have stable disease (SD) after a defined treatment period.

Phase III Trials. Phase III clinical trials represent the gold standard for drug development, and their size is based on appropriate statistically powered primary endpoints with additional secondary endpoints. These trials are required to be randomized with at least 2 arms, of which 1 can be a placebo or standard of care and the other can be the new drug or procedure. In order to find a statistical difference between arms, high numbers of patients (hundreds) are required, and must vary depending on the response rate. Because of the rare incidence of CTCL, only 2 randomized phase III clinical trials have been completed with systemic therapies, as shown in Table 2.[9,10] Both took over 10 years to accrue.[9] A third double-blind placebo-controlled phase III trial was conducted and randomized patients to topical vehicle versus topical peldesine cream.[11] No difference was found between the 2 arms, suggesting the beneficial effects of topical glycerin vehicle for early mycosis fungoides lesions.

Phase IV Trials. Phase IV trials are conducted after a drug is approved by the FDA. Some are mandated by the agency when preliminary approval of a drug is granted, in order to provide additional safety or efficacy information, and must be completed to gain full approval. The majority of phase IV studies are investigator-initiated trials in new indications or in novel combination with other agents. Phase IV studies can be driven by marketing and the need for other investigators to gain experience with a new drug. They are also conducted in order to better manage drug side effects, and often lack statistical significance in their design.

Practical Issues in Cutaneous T-Cell Lymphoma Clinical Trials

Design of Primary and Secondary Clinical Endpoints

Zacheim et al brought attention to adherence to defined endpoints for the conduct of CTCL trials back in 1996.[12] Bexarotene[6,7] and vorinostat[2,8] were approved on the basis of skin improvement by > 50% as the primary clinical endpoint but used different measurement tools. Progress is being made through the International Society of Cutaneous Lymphomas (ISCL) in developing well-defined consensus clinical response and endpoint criteria to allow standardized comparisons between different agents (Olsen, personal communication). These incorporate skin score into a composite score such as the one used in the approval of romidepsin. The modified skin-weighted assessment tool (mSWAT) is a primary clinical endpoint first used to measure skin involvement in denileukin diftitox trials.[10] It should be combined with clinical measurements of nodes, blood, visceral disease to assess systemic effect, ie, a global assessment of complete response (CR), partial response (PR), SD, and progressive disease (PD). In a global assessment, if there is disease progression in any of the compartments, then the effect is PD. Alternatively, all sites must have a complete remission for a CR designation. A skin biopsy should also be performed to confirm CR in skin. An index lesion evaluation, utilizing specifically designated skin lesions such as the composite index lesion assessment,[6] should only be used to assess effects of topical agents applied to specific skin lesions because the patient might progress outside of the graded areas index lesions.

Secondary endpoints may include time to response, duration of response, time to progression, symptoms, and assessments of quality of life. Erythema is sometimes given its own score and remains a key variable for assessing skin response. However, erythema can be ephemeral, and better ways of measuring erythroderma can be developed using technology. Finally, standards for assessing evaluable subjects or intent to treat analysis should be determined because responses will be lower in the latter group.

Another issue that should be addressed in clinical trials are the definitions of relapse (new lesions after a CR), loss of response (mSWAT score above the initial PR value), and PD. Progressive disease may be defined differently depending on whether the patient has achieved a response or not. If a patient has not responded, then PR is defined as a > 25%-50% improvement in the baseline mSWAT score and SD as < 25% worse from baseline. If the patient has responded, then a PD is best defined relative to the nadir rather