Abstract:
Most children with cancer are enrolled in a clinical trial, as progress is still needed for better treatments and improved prognosis. This can include phase I, II, or III trials, which vary from unknown adverse effects to well-established data. In the emergency department, it is critical to know if a patient is participating in a clinical trial and any known details or complications from the treatment. The present article reviews the fundamental foundation clinical trial phases, as well as possible adverse effects for patients enrolled on these studies.

Keywords:
clinical trial; phase; oncology; adverse effect

Clinical Trials 101 in Pediatric Oncology Patients

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Pediatric cancer is the leading cause of death by disease past infancy among children in the United States.[1] However, over the last several decades, overall survival rates for many pediatric cancers have greatly improved due in large part to clinical trials that have discovered new medications and/or drug combinations. Currently, most children with cancer are enrolled in clinical trials.[2] This can include phase I/II/III trials through single institutions, consortia, or most commonly the Children's Oncology Group. Clinical trials are vital in establishing data on safety and an evidence base to ensure optimal treatment for children diagnosed with cancer as well as to further improve the outcomes after treatment.

Although clinical trial details should not interfere with emergency department (ED) management, it is critical to understand the basic concepts and possible adverse effects if a patient is enrolled in a clinical trial. Any pediatric oncology patient presenting to the ED should be asked the following questions: type of cancer, presence of indwelling catheter (ie, central line), the type of treatment received to date (ie, surgery, chemotherapy, and/or radiation), enrollment on clinical trial, most recent antineoplastic therapy, and any known adverse effects or complications from that therapy.[3] As parents and patients have to remember a vast amount of information of the diagnosis and treatment plan, it may be difficult to gather all of the necessary information about types of treatment and details of the clinical trial. Therefore, we review the fundamental foundation of phase I, II, and III clinical trials, as well as possible adverse effects (See Table 1).

Phase I clinical trials seek to define a safe and appropriate dose of a new agent that can subsequently be used in phase II clinical trials.[4]

TABLE 1 Clinical trial phases.

Phase I
- Purpose: To evaluate a new drug or drug combination with respect to dose-limiting toxicities, maximum tolerated dose of the drug, as well as pharmacokinetics (ie, metabolism and elimination of the drug).
- Possible risks: unpredictable adverse effects

Phase II
- Purpose: To further evaluate safety and determine the effectiveness of the drug or drug combination against specific cancers using the dosage or schedule determined in phase I trials.
- Possible risks: unpredictable adverse effects

Phase III
- Purpose: To evaluate a new drug or combination in comparison with the current standard treatment, usually in a randomized fashion.
- Possible risks: New drug or combination may not be as beneficial as, or may be more toxic than, standard treatment.

Modified from Bond and Pritchard.[5]

These trials evaluate a new agent through assessment of toxicities, the maximum tolerated dose of the drug, as well as pharmacokinetics (ie, metabolism and elimination of the drug) and are conducted typically through a dose-escalation structure.[5] This is vital in pediatric oncology because toxic effects of drugs differ between children and adults. The effectiveness of the drug or drug combination is not a primary end point of these studies, although phase I studies are essential for developing new and innovative therapies in the field of pediatric oncology.[6] Many patients on phase I clinical trials have commonly failed other known therapies or have a cancer with limited effective treatment. Agents used in phase I trials may have generic names, whereas some agents are nondescriptive and abbreviated with letters and numbers (ie, AZD1775, LY2606368). This is important, as some families in the ED may not be able to explain exactly the details of the medication. Furthermore, the adverse effects are unknown and unpredictable in the ED setting.

Phase II trials play an important role in the assessment of treatment efficacy and relative safety of intervention and in identifying agents for further investigation in phase III studies. These trials, although experimental, are therapeutic in intent by evaluating drug efficacy, although benefit is not clearly demonstrated.[2] Many patients on phase II clinical trials have also commonly failed other known therapies or have a cancer with limited effective treatment. Phase II trials are likely to increase as more molecularly targeted agents and biologic agents become available.

Phase III trials study the efficacy and safety of a new drug or drug combination compared with the current standard treatment/schedule. This allows further evaluation and comparison of the agent for tumor response including event-free survival, time to progression, and/or overall survival.[5] Most patients on phase III trials are newly diagnosed patients. Whereas phase I and II trials recruit less than 100 patients, phase III trials are large with hundreds to thousands of patients.[2]

Most phase III trials are done in a randomized fashion with half of the comparative group receiving conventional cytotoxic chemotherapy. All of these agents have adverse effects that may warrant evaluation in the ED. The benefit of this group of patients in the ED setting is that the adverse effects are well known. Most of these agents cause myelosuppression, nausea, vomiting, and mucositis, with additional adverse effects found in detail in Table 2.

Over the last decade, newer targeted biologic and antiangiogenic agents have been at the forefront of clinical trials. Their development focuses on specific changes that alter the malignant cell, that is, genetic mutations, genetic rearrangements, epigenetic modifications, lineage legacies, and/or other metabolic liabilities.[2] This includes new hormone therapies, signal transducer inhibitors, gene expression modulators, apoptosis inducers, angiogenesis inhibitors, immunotherapies, monoclonal antibodies, cancer vaccines, and gene therapy. An advantage of such targeted therapy is the link between target inhibition and efficacy, with dosing goals based on target inhibition rather than maximum tolerated dose. This suggests that adverse effects should not be as toxic and are more predictable, although adverse effects are still substantial and can lead to ED evaluation. Currently, adverse effects are still largely based on adult experience or in early phases of pediatric clinical trials and thus lack clear demonstration of efficacy and toxicity. In adults, adverse effects of targeted cancer therapies include nausea, diarrhea, liver dysfunction (ie, elevated liver enzymes, hepatitis), dermatologic changes, allergic reaction, edema, hypertension, delayed wound healing, bleeding, and/or hyperviscosity.[7] Additional adverse effects in children may include immunosuppression (although not as severe as cytotoxic chemotherapy), flu-like symptoms (ie, fever, chills), hypothyroidism, shortness of breath, headache, and/or dizziness.[8] Although these clinical trials and medications are constantly evolving, Table 3 lists a few of the common pediatric targeted treatments currently used with possible adverse effects.