Understanding clinical trials in childhood cancer

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Clinical trials in paediatric cancer continue to be a key factor in progress toward better treatment and prognosis. Paediatricians and family physicians may be asked by patients and families for their advice regarding participation in such trials. The significant advances in the success of treatment of paediatric cancer have come, in part, from the high participation rate of patients in such studies. The present article reviews the definitions and goals of phase 1, 2 and 3 trials. A known and trusted physician or paediatrician can be helpful in conjunction with the oncologist in guiding patients and their families and helping them understand the risks and benefits of participation in clinical trials.

Key Words: *Cancer; Children; Trials*

Comprendre les essais cliniques sur le cancer chez les enfants

Les essais cliniques sur le cancer pédiatrique continuent d'être un élément essentiel des progrès vers un meilleur traitement et un meilleur pronostic. Les patients et leur famille peuvent demander conseil aux pédiatres et aux médecins de famille quant à leur participation à ces essais. Les importants progrès dans le succès des traitements du cancer pédiatrique sont partiellement attribuables au fort taux de participation des patients à ces études. Le présent article analyse les définitions et les objectifs des essais de phases 1, 2 et 3. Conjointement avec l'oncologue, un médecin ou un pédiatre connu et de confiance peut orienter les patients et leur famille et les aider à comprendre les risques et les bienfaits d'une participation à des essais cliniques.

Cancer is the second leading cause of death in children after trauma (1,2). Although paediatric cancer is uncommon, accounting for less than 1% of all cancers, the benefit in terms of life-years saved as a result of paediatric cancer cures is high. Remarkable progress has been made in the past two decades; more than 75% of children diagnosed with cancer today will be long-term survivors (3-5). This progress is largely the result of high participation rates in well-organized multicentre clinical trials. An analysis of National Cancer Institute (NCI) Cooperative Group trial enrolment from 1998 to 1999 showed that approximately 2.5% of adult cancer patients participate in clinical trials, while 50% of children aged zero to 14 years old participated.

PHASES OF CLINICAL TRIALS

Clinical trials have as their primary goal the improvement of future treatment. Clinical cancer research involves testing new agents, combinations and treatment programs in an orderly series of steps or phases (6) (Table 1).

Phase 1 clinical trials evaluate a new drug to determine its maximum tolerable dose; toxicities (including the dose limiting toxicity); and the metabolism and elimination of the agent (pharmacokinetics). Some early evidence of antitumour activity is also sought. Participants have usually failed known active treatment or have a tumour for which there is no known active agent. Adequate organ function is usually also required to allow valid assessment of toxicity associated with the agent being tested. Phase 1 trials may include not only first trials of a new agent in paediatric medicine but also new schedules or combinations of agents (7).

Phase 2 trials evaluate the efficacy of an agent against a specific tumour, in a dose and schedule determined in a phase 1 trial. The outcome to be evaluated is usually tumour response. Tumour response does not necessarily imply improved event-free survival, time to progression of cancer or overall survival. These effects are tested in phase 3 settings.

Paediatric cancer patients are precious resources because, as previously noted, their numbers are small. As a result, investigators are obliged to carefully select projects based on their likelihood of succeeding because not every potential agent or combination can be tested. New agents have usually been previously tested and found to be useful in adult cancer patients. Agents may also be chosen for testing when preclinical models suggest a specific activity against paediatric tumours or based on a novel mechanism of action or favourable drug-resistance profile (8,9). Drug availability or predicted future drug availability is an important factor in the selection of agents for paediatric trials. Because paediatric cancers are uncommon, agents that are also effective in adult cancer types are more likely to continue to be produced.

Phase 1 and phase 2 clinical trials are experimental trials and are not expected to result in a cure. Access to paediatric phase 1 studies in Canada is limited to only a few centres. Participation in a phase 1 study requires that the patient be treated at the institution that registered the patient. For many families, participation could involve taking the child to another province or out of country. 'Out of province' or 'out of country' treatment in a phase 1 study is

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unlikely to be paid for by provincial medical plans. Most tertiary care paediatric oncology centres in Canada participate in phase 2 trials, but eligibility is limited, as is the selection of available trials. Because this treatment is not of proven efficacy, 'out of province' or 'out of country' participation is also unlikely to be funded by provincial medical plans.

Phase 3 trials evaluate a new drug or drug combination in comparison with the current standard treatment, usually in a randomized fashion. Phase 3 trials include a control arm, which represents the current best treatment, and an experimental arm, which has additional treatments or has been tested in a phase 2 setting. Although there is an expectation that the experimental arm is effective and at least as good as the standard treatment, there is no confirmed evidence that it is better. The experimental arm may also be found to be less effective or more toxic than the standard treatment. Patients are usually randomly assigned to a specific treatment arm, which is necessary to avoid selection bias. An example of such a bias is preferentially assigning patients with less disease to the easier treatment. Randomization also tends to produce treatment groups in which the distributions of prognostic factors, known and unknown, are similar. The treatment end points are usually event- or relapse-free survival and overall survival. Although these clinical trials may not directly benefit the participants, there is a suggestion that participants as a group do as well as or better than children treated on standard treatment outside the clinical trial setting (10-12). The reason for this is not completely known nor is the validity of this observation unchallenged (13). This may be a participation effect, with patients benefiting from the strict treatment and monitoring guidelines used in clinical trials. Alternatively, the observation of benefit with participation may be a result of the group's baseline characteristics or biases in data collection and reporting.

ORGANIZATION OF PAEDIATRIC CLINICAL TRIAL NETWORKS

Paediatric clinical research may be generated and performed by single institutions. However, because patient numbers are limited, few centres have sufficient patients and multi-institutional clinical research predominates. All paediatric cancer treatment centres in Canada are members of the Children's Oncology Group (COG). COG is an NCI-supported clinical trials cooperative group devoted exclusively to childhood and adolescent cancer research. COG develops and coordinates cancer clinical trials conducted at the 238 member institutions, including cancer centres of all major universities and teaching hospitals throughout Canada and the United States, as well as sites in Europe and Australia.

Recently, the Council of Canadian Pediatric Hematology Oncology Directors (CCPHOD) has developed a Canadian clinical trial network facilitating clinical trials involving patients at Canadian institutions. Clinical trials supported by this network are not competing with those of COG. Canadian paediatric oncology centres consider COG to be their primary clinical trial network.

TABLE 1
Characteristics of phase 1, 2 and 3 clinical trials

Phase 1 clinical trials
Purpose
• To evaluate a new drug, drug combination or treatment schedule with respect to:
◦ maximum tolerable dose as determined by increasing the dose of drug with each cohort of participants;
◦ dose limiting toxicities;
◦ metabolism and elimination of the drug; and
◦ antitumour activity within the confines of a phase 1 study. The effectiveness of the drug or drug combination is not a primary end point of these studies.
Eligibility
• Patients must have failed known active treatment.
• Patients must have adequate organ function and a life expectancy of at least eight weeks.
Possible risks
• Unpredictable side effects.
Possible benefits
• Possible anticancer effect.
Restrictions
• Phase 1 studies are usually restricted to 15 to 30 patients.
• Studies are conducted at a limited number of specialized institutions.
Phase 2 clinical trials
Purpose
• To determine the effectiveness of the drug or drug combination against specific tumours using the dosage or schedule determined in phase 1 studies.
• To further evaluate safety.
Eligibility
• Patients who have failed standard treatment.
• Patients who have a tumour with no known effective treatment.
Possible risks
• Unpredictable side effects.
• No anticancer effect.
Possible benefit
• If the drug has anticancer effects, the study subjects may be among the first to benefit.
Restrictions
• Phase 2 studies are usually restricted to approximately 100 patients.
• Studies are conducted at a limited number of specialized institutions.
Phase 3 clinical trials
Purpose
• To evaluate a new drug or combination in comparison with the current standard treatment, usually in a randomized fashion.
Eligibility
• Newly diagnosed patients.
Possible risks
• New drug or drug combination may not be as good as, or may be more toxic than, standard treatment.
Possible benefits
• If new drug(s) are better, study subjects may be among the first to benefit.
• Participation in the clinical trial may result in improved outcome because of strict monitoring guidelines.
Restrictions
• Phase 3 trials recruit several hundred to several thousand patients. They are multicentred, including many community centres.

QUALITY AND SAFETY

Cooperative group projects are reviewed both by the group and by its NCI or CCPHOD sponsors to ensure that the projects are scientifically valid. These same tasks are

assumed by local institutions if projects are generated 'in house'. All Canadian clinical trials testing new medications or testing known medications outside the approved indications – whether locally initiated, part of a clinical trial network or industry sponsored – are also reviewed by Health Canada (14). All investigators are required to conduct their studies in accordance with the good clinical practice consolidated guidelines, which include the requirement for quality in all aspects of the clinical trial, including monitoring of unexpected side effects and results (15). Trials are stopped early if there are significant toxicities or if one arm is clearly more or less effective than the others.

INDUSTRY-SPONSORED CLINICAL TRIALS

Pharmaceutical companies may be involved in clinical trials in two ways. They may sponsor some part of a trial being conducted by a cooperative group or a local investigator. Alternatively, often as part of licensing requirements, a trial may be initiated, developed and conducted by a pharmaceutical company with the help of a local investigator. The pharmaceutical sponsor may ask for a degree of confidentiality from the local investigator, particularly for trials initiated by the sponsor. In both situations, the research will be reviewed by local institutional review boards (IRBs) and cannot be conducted unless approved.

ETHICS OF CLINICAL TRIALS IN CHILDREN

A clear understanding of the goal of a clinical trial, as well as the potential risks and benefits of participation, is essential to the ethical conduct of a clinical trial, as is the understanding that participation in a clinical trial is voluntary and never a condition for receiving the best possible care and treatment.

There is a recognized concern that physicians, patients and families may overestimate the therapeutic benefit of participation in clinical trials, particularly phase 1 and 2 trials (16). The accurate and complete communication of these issues, both by discussion and by documentation, constitutes the informed consent process. Parents usually find the consent process satisfactory and discussions more helpful than the actual consent document (17). As a result of the often urgent nature of the disease, children with cancer and their parents may be asked to participate in a trial immediately after diagnosis. A known, trusted physician or paediatrician can be helpful in conjunction with the oncologist in helping them understand the risks and benefits of participating in the study.

Investigators at each participating site are required to seek and obtain approval from their IRB, whose mandate is to ensure that the project protects patients' rights with respect to its conduct and informed consent procedures. These boards are required by Health Canada to adhere to principles outlined in "Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans" (18). No patient should be enrolled in a trial that has not received approval from the local IRB.

CONCLUSION

It is certain that past clinical cancer research trials have resulted in benefit to today's children. Future progress depends on continued participation in clinical trials. Family physicians and paediatricians may be asked by the families of their patients for advice. A thorough understanding of the clinical trial system is necessary to counsel patients and families who may be asked to, or may wish to, participate.

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