CAN CANADA SUSTAIN PAEDIATRIC PHASE I TRIALS? A NATIONAL SURVEY OF CANCER RELAPSE IN CHILDREN

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ABSTRACT

Background
Paediatric phase I trials are critical to the evaluation of new agents using standardized methodology. However a large proportion of paediatric patients in Canada do not have access to phase I therapy.

Objectives
A National Paediatric Cancer Relapse Survey was conducted to collect preliminary data to evaluate the feasibility of multi-centre paediatric phase I trials within Canada.

Methods
A survey consisting of 20 individual questions was sent out to all of the 17 paediatric oncology centres in Canada.

Results
Fifteen centres (88%) responded to the survey. 1027 children are diagnosed with cancer each year in Canada while 241 present with recurrent cancer. Of the 85 patients who are considered to be eligible for phase I study each year, only 53% were referred for phase I therapy. Two centres have more than 10 eligible patients a year, while the remaining 13 centres have less than 10 eligible patients each year.

Conclusions
We estimate that 20% of the eligible patients could be accrued to phase I trials and Canada may provide sufficient patient number, i.e. 25 to 30 solid tumour patients every 2 years, to allow one multi-centre paediatric phase I trial to be completed over a 2-year period.

Key Words: *Neoplasms, recurrence, paediatrics, Canada, phase I clinical trials*

Advances in cancer therapy over the past several decades allow the majority of children with cancer to be cured. However, 20 to 30% die as a result of refractory disease or complications of toxic therapy.[1] In addition, 20% of long-term survivors of childhood cancer are affected by late complications of anti-cancer therapy.[2] Hence, there remains a need for new anti-cancer agents, which are more effective and less toxic. Since neither pharmacokinetics nor toxicities experienced in adult phase I studies can be safely extrapolated to children, paediatric phase I trials are therefore critical to the evaluation of promising new agents using standardized methodology.[3, 4] The main objectives of paediatric phase I trials are to define a safe and appropriate dose and schedule for new agents that can be subsequently used in phase II trials to test for activity against specific childhood cancers and to characterize the nature and frequency of the toxicities in children receiving the new agents.[4] Almost all new agents tested in paediatric phase I

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studies have gone through adult phase I trials, which provide valuable information on drug toxicities in human subjects and help in the design of paediatric trials. The eligibility criteria for entry of children into phase I trials demand that all conventional treatment has failed or no standard therapy exists and require a life expectancy of at least 6 to 8 weeks, in addition to adequate organ function and performance status.[3] Since cancer in children is rare (incidence of 140 per million)[1] and the cure rate is relatively high, only a small number of paediatric patients fulfil the eligibility criteria of phase I trial. An even smaller number will be accrued as the majority of parents/guardians will not consent to phase I experimental therapy.

In Canada, approximately 1,300 children between the ages of 0 and 19 years are diagnosed with cancer and about 220 die from cancer each year.[5, 6] These children are treated at one of the 17 paediatric oncology centres across Canada. All 17 Canadian centres are members of the Children's Oncology Group (COG), which conducts multi-centre clinical trials at 247 member institutions throughout North America, Europe and Oceania. [7] Within COG, the COG Phase I/Pilot Consortium develops phase I trials, which are then implemented in 21 phase I institutions. Only two of these phase I institutions are in Canada (Hospital for Sick Children, Toronto and Hôpital Sainte-Justine, Montreal). A Canadian child who has refractory cancer and is eligible for an open phase I study can either be treated at one of the two Canadian centres or be referred to a U.S. centre. But it is not hard to understand why it is neither feasible nor ethical to refer a child, who has end-stage cancer and does not reside within reasonable proximity to Toronto or Montreal, for phase I therapy in Canada or in the U.S. Furthermore, for an eligible Canadian child to receive phase I treatment in the U.S, the family will have to bear the medical expenses since costs related to experimental therapeutics outside of Canada are not covered by the provincial governments responsible for financing health care in Canada.

We therefore raised the question whether national multi-centre paediatric phase I trials, which allow patients to receive phase I therapy in most Canadian centres, are feasible in Canada. Although statistics on cancer incidence and mortality are readily available from Health Canada, it is unclear how many children develop recurrent or refractory cancer across Canada each year, the specific type of cancer they have and how many of these children will fit the eligibility criteria of phase I trial. Hence we conducted a National Paediatric Cancer Relapse Survey with an objective to collect preliminary data to answer these questions, to explore interest in a National Developmental Therapeutics initiative and to evaluate the feasibility of initiating a Canadian Paediatric Cancer Relapse Registry.

METHODS

A survey consisting of 5 parts (demographics, statistics, access, human resources and comments) with a total of 20 individual questions was sent out to the 17 Canadian paediatric oncology centres listed in Table 1. The content of the survey is summarized in Table 2.

RESULTS

Fifteen centres (88%) responded to the survey. The 3 questions related to types of cancer (question 3b, 4b and 5b) were not answered by all 15 centres. Question 3b (new diagnoses subtypes) was omitted by 1 centre, question 4b (relapse subtypes) by two centres and question 5b (eligible Phase I subtypes) by four centres.

The survey indicates that 1027 children are diagnosed with cancer each year at the 15 Canadian centres responding to the questionnaire, while 241 children present with recurrent cancer. Over 60% of both new diagnoses and relapses are reported in Ontario and Quebec. Eighty-five patients are estimated to be eligible for phase I studies each year (Figure 1) and consist of 38% solid tumours (n=32), 33% brain tumours (n=28), 20% leukaemia (n=17), and 9% lymphoma (n=8). Eleven centres have fewer than five patients eligible for Phase I trials per year and two centres have 5 to 10 eligible patients.

The two COG phase I institutions (The Hospital for Sick Children and Hopital Sainte-Justine), which are the only two centres with their own developmental therapeutics program, have more than 10 eligible patients per year. Only 45 (53%) of these eligible patients have access to phase I therapy. This include 35 patients (41%)

from the two phase I centres and another 10 (12%) referred from four nearby centres (Kingston, Ottawa, Montreal, Sherbrooke). Only these four centres have referred their patients with recurrent disease to the two Canadian centres for phase I therapy over the last 12 months. Eleven centres expressed an interest in a National Developmental Therapeutics initiative. Five centres have access to both tumor bank and a pharmacokinetics laboratory, one to tumor bank alone and one to pharmacokinetics laboratory only. The 6 pharmacokinetics laboratories are distributed over 5 provinces (British Columbia, Alberta, Ontario, Quebec and Nova Scotia). Only one center has a dedicated onco-pharmacology laboratory (Hospital for Sick Children).

Human resources range from 1 to 23 full time equivalent (FTE) physicians per centre with a total of 80.5 FTE paediatric haematologist/oncologists among the 15 responding centres in Canada and 0.5 to 10 FTE clinical research assistants per centre (total 45.0 in Canada).

TABLE 1 Seventeen paediatric oncology centres in Canada

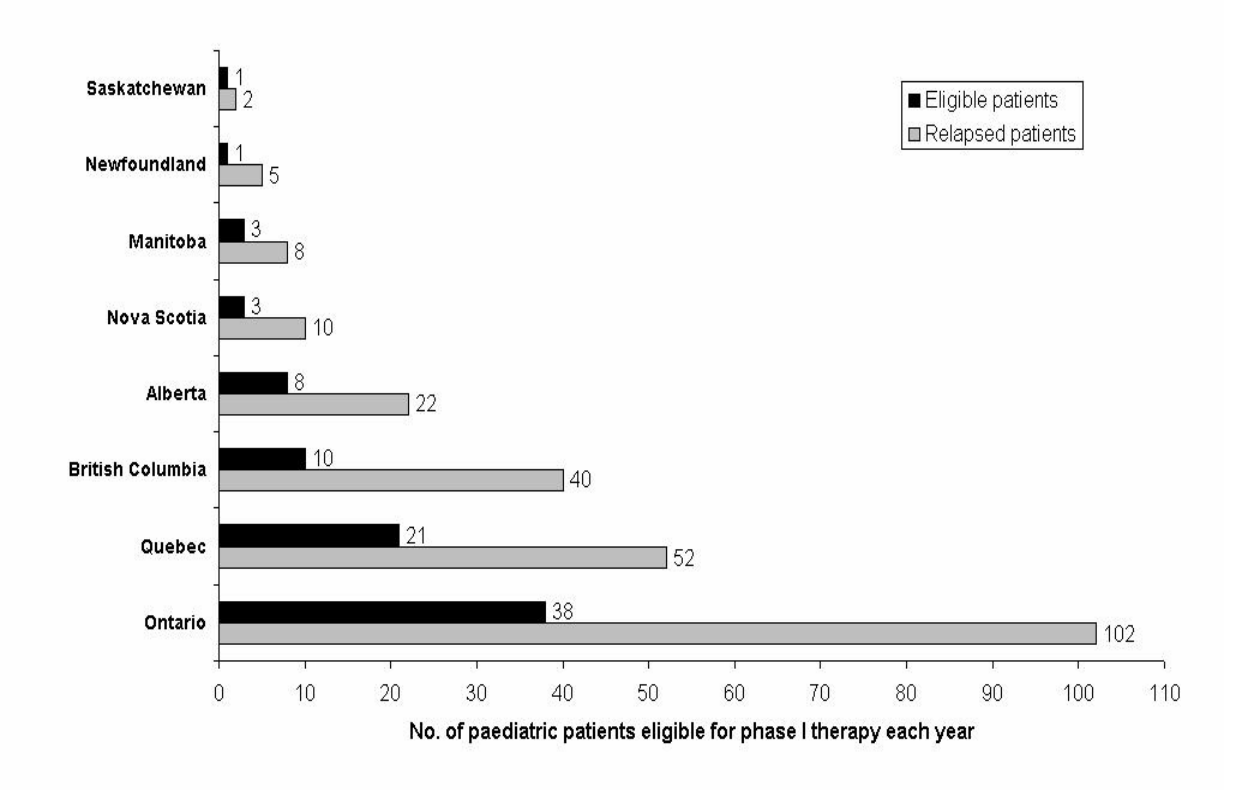
Province	City	Centre
British Columbia	Vancouver	British Columbia's Children's Hospital
Alberta	Calgary	Alberta Children's Hospital
	Edmonton	Stollery Children Hospital
Saskatchewan	Saskatoon	Saskatoon Cancer Centre
	Regina	Allan Blair Cancer Centre
Manitoba	Winnipeg	CancerCare Manitoba
Ontario	London	Children's Hospital of Western Ontario
	Hamilton	Children's Hospital at Hamilton Health Sciences
	Toronto	The Hospital for Sick Children *
	Ottawa	Children's Hospital of Eastern Ontario
	Kingston	Kingston General Hospital
Quebec	Sherbrooke	Centre hospitalier universitaire de Sherbrooke
	Ste Foy	Centre hospitalier de l`Université Laval
	Montreal	Hôpital Sainte-Justine *
	Montreal	Montreal Children's Hospital
Nova Scotia	Halifax	IWK Health Centre
Newfoundland	St John's	Janeway Child Health Centre

* Children's Oncology Group (COG) phase I institution

TABLE 2 National Paediatric Cancer Relapse Survey

I.	**Demographics**
1.	Province, Institution, Principle Investigator
2.	Do you have a Developmental Therapeutics Program within your department?
	If no, are you interested in a National Developmental Therapeutics initiative?
II.	**Statistics**
3a.	How many newly diagnosed patients on average per year are there?
b.	And how many new patients are there in each of the 4 groups: leukaemia, lymphoma, solid tumor, brain tumor?
4a.	How many relapses on average per year are there?
b.	And how many relapses are there in each of the 4 groups: leukaemia, lymphoma, solid tumor, brain tumor?
5a.	How many relapsed patients per year would be eligible for Phase I therapy?
b.	And how many eligible patients are there in each of the 4 groups: leukaemia, lymphoma, solid tumor, brain tumor?
III.	**Access**
6a.	What is the closest Canadian Phase I centre to you?
b.	How many patients were referred to a Canadian centre for Phase I therapy in the last 12 months?
c.	And how many patients were referred in each of the 4 groups: leukaemia, lymphoma, solid tumor, brain tumor?
7a.	What is the closest U.S. Phase I centre to you?
b.	How many patients were referred to a U.S. centre for Phase I therapy in the last 12 months?
c.	And how many patients were referred in each of the 4 groups: leukaemia, lymphoma, solid tumor, brain tumor?
8.	Does your department have access to a tumor bank?
9.	Does your department have access to a pharmacokinetics laboratory?
IV.	**Human Resources**
10.	How many MD's (full time equivalent) are there in your department?
11.	How many clinical research assistants (full time equivalent) are there in your department?
12.	What is your department's specific area of interest/expertise?
V.	
13.	Comments

FIGURE 1. Geographical distribution by province of the 241 paediatric patients diagnosed with recurrent cancer each year and the 85 patients eligible for paediatric phase I trials each year in Canada.



DISCUSSION

Phase I trials represent a safe mechanism to obtain valuable information on toxicity and pharmacokinetics of new agents in children with cancer and are critical to the rational introduction of new therapies in paediatric oncology. A recent review of 28 paediatric phase I trials reported a drug-related toxic death rate of 0.56% and 21% of the patients experienced dose-limiting toxicity.[8] A major obstacle to the development of paediatric phase I trials is the small number of paediatric patients who are available for phase I studies. This small number is reflected by a total of only 26 published articles on single agent paediatric phase I trials worldwide between 1990 and 1996; moreover only 6 of the 22 evaluated agents are used today.[9]

In Canada, this small population is further reduced since access to phase I therapy is restricted to the two paediatric phase I institutions in Toronto and Montreal. As a result, a significant proportion of paediatric oncology patients in Canada, despite being eligible for phase I studies, are not referred for phase I therapy. Our survey estimates that of the 241 children with recurrent cancer each year, 85 (35%) would be eligible for Phase I trial and 40 (47%) of the 85 eligible patients do not have access to phase I study.

Using the figures from this survey, 32 children with refractory solid tumour, 28 with brain tumour, 17 with leukaemia and 8 with lymphoma could be eligible for phase I studies each year in Canada. If we are to evaluate a new agent for refractory solid tumours, including both extra-cranial solid tumours and central nervous system tumours, then 60 patients will be eligible each year. Not infrequently, lymphoma is also included in solid tumour phase I trials.[10, 11] However, the actual number of patients that will ultimately be accrued is significantly less. An open phase I trial may have specific eligibility

criteria related to the profile of the phase I agent being tested and not all patients who fulfil the standard or common criteria of phase I study will be eligible for the particular phase I study open at a given time point. Furthermore a phase I trial accrues patients in small cohort of three patients and must be temporarily suspended to allow toxicity to be fully evaluated at each dose level. Thus potentially eligible patients cannot be enrolled during the suspension period. From our personal experience in conducting paediatric phase I trials, only 20% of the eligible patients will be accrued to a pediatric phase I trial. Therefore we estimate that 12 to 15 "solid tumour" patients can be accrued in Canada each year. Since the starting dose of a paediatric phase I trial is commonly set at 80% of the maximum tolerated dose (MTD) determined in adult phase I trial, a paediatric phase I trial generally requires evaluation of fewer that five dose levels and only 25 to 30 patients are needed to complete a paediatric phase I trial.[9] Combining these figures, we estimate that Canada can provide sufficient patient numbers, i.e. 25 to 30 solid tumour patients every 2 years, to allow one multi-centre paediatric phase I trial to be completed over a 2-year period.

The main objective of this survey was to collect preliminary data on paediatric cancer recurrence, which is essential for determining the feasibility of establishing a National Developmental Therapeutics initiative. Data collected in this survey is derived from institutional records and database, the same channel through which statistics submitted to provincial and national tumor registries originate from. The validity of this preliminary data is supported by the high participation rate of 88% and figures comparable to statistics released by Health Canada.[5, 12] The two centres that did not respond are small institutions; each would have less than 5 patients eligible for phase I studies each year. We estimate that if these two centres had responded, the total number of eligible patients would only have increased marginally and would not change our conclusions. Except for the 3 questions on types of cancer, the other 17 questions were answered completely by all respondents. Since it is unlikely that there is a significant variation in the different types of childhood cancer managed by each institution, the information on distribution of types of cancer should be valid.

This survey provides encouraging preliminary data, suggesting that there may be sufficient patient number to sustain paediatric phase I trials in Canada, based on an estimated accrual rate of 20% amongst eligible patients and a sample size of 25 to 30 patients. The availability of pharmacokinetics laboratories and most important of all, interest expressed by almost all centres are also encouraging factors. However an accrual rate of 20% may have been overestimated and inevaluable patients mean additional patients need to be enrolled to complete the trial. Hence there may be too few eligible patients to justify a national program with a portfolio of paediatric phase I trials. However we believe that one to two ongoing national phase I studies in selected indications such as leukemia/lymphoma and solid tumours including brain tumours may still be feasible. More accurate and specific data on paediatric cancer recurrence are needed. This is most efficiently done by collecting data prospectively using a registry and requires collaboration among paediatric oncology centres. We hope that participation in the registry will heighten the awareness and interest in phase I trials in the pediatric oncology community and possibly improves accrual rate. Opening a clinical trial in any health institution requires tremendous effort and cannot be initiated if clinicians lack interest, especially in the setting of a small centre. If the final decision is to open paediatric phase I trials in Canada, such group effort will prove valuable since collaboration is crucial to the development of the structure and mechanisms to undertake multi-center studies. On the other hand, if prospective registry data indicates that there will be insufficient patient number to implement multi-center paediatric phase I trials within Canada, resources should be directed towards continual collaboration with North American groups and initiation of collaboration with European groups.

As paediatric oncologists, we recognize the need of evaluation of new agents in children with cancer and that the rational introduction of new therapies can only be achieved by starting with phase I studies and working closely with

pharmaceutical sponsors and regulatory agencies. We propose the creation of a National Developmental Therapeutics initiative with the establishment of a Canadian Paediatric Cancer Relapse Registry as the first step of this initiative.

We hope that if registry data support the viability of paediatric phase I trials in Canada, a Canadian Paediatric Phase I Consortium may evolve to implement phase I studies in a safe and ethical manner. Ultimately collaboration, whether at a national or international level, is crucial for the implementation of paediatric phase I trials with the specific aim to facilitate the integration of advances in cancer biology into the treatment of childhood cancer.

APPENDIX Council of Canadian Paediatric Haematology/Oncology Directors

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REFERENCES

1. Smith MA, Gloeckler Ries LA. Childhood cancer: incidence, survival, and mortality. In: Pizzo PA, Poplack DG, ed. Principles and practice of pediatric oncology. 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2002:1-12.
2. Mertens AC, Yasui Y, Neglia JP, et al. Late mortality experience in five-year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study. *J Clin Oncol* 2001;19(13):3163-72.
3. Pratt CB. The conduct of phase I-II clinical trials in children with cancer. *Med Pediatr Oncol* 1991;19(4):304-9.
4. Smith M, Bernstein M, Bleyer WA, et al. Conduct of phase I trials in children with cancer. *J Clin Oncol* 1998;16(3):966-78.
5. Health Canada. Cancer surveillance on-line. Cancer incidence by age group. http://dsol-smed.hc-sc.gc.ca/dsol-smed/cgi-bin/cancerchart2?DATA_TYPE=D&AGE_GROUPS=T%3BU%3BV%3BW&CAUSE2=019&YEAR2=00&AREA2=00&SEX2=3&CAGE2=View+Chart&SCALE=LINEAR (May 18, 2004).
6. Health Canada. Cancer surveillance on-line. Cancer mortality by age group. http://dsol-smed.hc-sc.gc.ca/dsol-smed/cgi-bin/cancerchart2?DATA_TYPE=D&AGE_GROUPS=T%3BU%3BV%3BW&CAUSE2=019&YEAR2=00&AREA2=00&SEX2=3&DATA_SET=MORT&CAGE2=View+Chart&SCALE=LINEAR (May 18, 2004).
7. National Childhood Cancer Foundation. Childhood cancer treatment and research centers. http://www.nccf.org/help/references.asp?cat=13&catName=CHILDHOOD%20CANCER%20TREATMENT%20AND%20RESEARCH%20CENTERS#results (May 18, 2004).
8. Estlin EJ, Cotterill S, Pratt CB, Pearson AD, Bernstein M. Phase I trials in pediatric oncology: perceptions of pediatricians from the United Kingdom Children's Cancer Study Group and the Pediatric Oncology Group. *J Clin Oncol* 2000;18(9):1900-5.
9. Shah S, Weitman S, Langevin AM, Bernstein M, Furman W, Pratt C. Phase I therapy trials in children with cancer. *J Pediatr Hematol Oncol* 1998;20(5):431-8.
10. Langevin AM, Weitman SD, Kuhn JG, et al. Phase I trial of rebeccamycin analog (NSC #655649) in children with refractory solid tumors: a pediatric oncology group study. *J Pediatr Hematol Oncol* 2003;25(7):526-33.
11. Wells RJ, Reid JM, Ames MM, et al. Phase I trial of cisplatin and topotecan in children with recurrent solid tumors: Children's Cancer Group Study 0942. *J Pediatr Hematol Oncol* 2002;24(2):89-93.
12. Health Canada. Cancer surveillance on-line. Cancer incidence by site. http://dsol-http://dsol-smed.hc-sc.gc.ca/dsol-smed/cgi-bin/cancerchart2?DATA_TYPE=D_HBAR1&CAUSE=ALL&YEAR=00&AREA=00&AGE=T&SEX=2&CCAUSE1=View+Chart (May 18, 2004).