Clinical Trial Perspective
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CLINICAL INVESTIGATION

Can we improve the efficiency of early phase trials in pediatric oncology?

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Despite significant improvement in survival for childhood cancer, there remains an urgent need for novel therapies for poor risk cancers and to reduce the burden of treatment for survivors. We analyzed the efficiency of published early phase clinical trials over the past two decades and found a modest increase in the number of both trials and agents studied, with a significant move from cytotoxic chemotherapy to oral based targeted agents. However, there has been limited adoption of new design methodologies. We believe that combined Phase I/II studies with an initial dose-escalation (proof of mechanism) phase followed by an integrated Phase II (proof of concept) to demonstrate direct clinical benefit could greatly improve the efficiency of early clinical trials in pediatric oncology.

Keywords: cancer • child • clinical trials • pediatric oncology • Phase I • Phase II

Survival in childhood cancer has significantly improved over the past 40 years as a result of clinical trials by cooperative child cancer networks and the optimization of multimodality anticancer therapy including surgery, radiotherapy and chemotherapy [1]. However, recent progress in some tumor types has been minimal or nonexistent plus there is a need to reduce the treatment burden and long-term side effects experienced by children with cancer [2]. Therefore, there is a desperate need for novel anticancer therapies to further improve survival rates and to replace more toxic standard treatments. Early clinical trials are an essential component in the drug development process of new cancer agents and traditionally is comprised of Phase I and Phase II trials. The aims of Phase I trials are to establish a safe dose and characterize the toxicity profile usually in a relapsed population; they often include pharmacokinetic sampling and a preliminary assessment of tumor response. Phase II trials commence following the establishment of a recommended dose (RP2D) and treatment schedule from Phase I and the primary aim is to formally assess antitumor activity, to further document the safety profile and is the critical point when a decision is made to move to Phase III trials. Recommendations about the conduct of Phase I trials in children with cancer were agreed over 15 years ago and although based in the era of conventional cytotoxic chemotherapy trial design has changed little since that time [3]. In the past decade, the explosion in the knowledge of the underlying molecular basis of cancer has resulted in the majority of novel therapies being biologically targeted agents and adaptions in early phase clinical trial design have been suggested to reflect the specific needs of these therapies in adult oncology [4,5]. The introduction of biomarkers to determine patient selection and establish optimal biological dosing has aimed to improve the efficiency of early clinical trials and has resulted in recommendations as to how best validate and incorporate them into the drug development process [6,7].

The most efficient early clinical trials in pediatric oncology would result in the identification of a safe and tolerable dose and to confirm or exclude significant clinical activity by using as few patients and in the shortest time possible. In order to study the efficiency

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of the drug development process in childhood cancer one needs to evaluate the following key elements: number of new agents and Phase I trials studied. For Phase I studies: the number of patients enrolled and dose levels studied plus the time to complete. The percentage of Phase I studies for a new agent that have a corresponding Phase II and the time interval between Phase I and II trials. We therefore undertook a review of published Phase I clinical trials in childhood tumors to investigate the above key elements and explore whether there had been any changes in trial design or practice over time, which may have altered the efficiency of early phase clinical trials in childhood cancer.

Methods

The online databases MEDLINE, Embase and PubMed were interrogated for published pediatric oncology Phase I studies over a 20 year period (1993 to 2013) using the following MeSH search terms: child, pediatrics, oncology, cancer, neoplasm, tumor, clinical trial and Phase I. The following predetermined inclusion criteria were used to select Phase I trials for further analysis; published in peer review journal, single agent (combination with radiotherapy allowed), solid tumors and brain tumors ± hematological malignancies and English language. The following predetermined exclusion criteria were then applied; multi-agent studies, trials of hematology-only, bone marrow transplant-only, radiotherapy-only, supportive care, cellular therapeutics (we specifically excluded immunotherapy studies as we believe these require different methodologies), mixed adult and pediatric population or conference proceedings/abstract only. All eligible publications were then analyzed for the main clinical trial design features using descriptive statistics. Statistical analysis was conducted (STATA v11.2 software) to explore possible changes in design and outcome over two decades (1993–2003 vs 2004–2013) using the Fishers exact to test for statistical significance. In order to determine how many Phase I agents progressed to Phase II trials and the time interval for this to occur, all anticancer agents identified through the above search strategy, had a second subsequent search conducted for the first corresponding Phase II trials (active or closed) using the following resources:

- http://clinicaltrials.gov
- www.cancer.gov/clinicaltrials
- www.ncbi.nlm.nih.gov/pubmed

Results

The outlined search strategy found 126 published Phase I studies meeting our criteria between 1993 and 2013 (a complete listing and associated references is provided in Supplementary Table 1). Table 1 shows the trials main features by decade of publication. The 126 Phase I trials studied 90 investigational agents. Over the last decade (2004–2013) there have been more trials (75 vs 51) and more agents studied (60 vs 35) compared with the previous 10 years. Other significant trends in the most recent decade are an increase in oral agents, and a change from conventional cytotoxic chemotherapy to more targeted anticancer agents being studied in Phase I trials. The design of pediatric oncology Phase I trials has also changed with newer methods such as the continuous reassessment method (CRM) and the 'rolling 6' starting to be used instead of the classical 3 + 3 cohort methodology in more recent trials. The inclusion of a dose expansion cohort or even a statistically powered Phase II component as part of the initial trial has also emerged as a new design feature in the last decade. The majority of Phase I studies still have a mixed population of childhood cancer types including solid and CNS tumors, but increasingly over the past 10 years Phase I trials may now restrict to either CNS tumors or a specific solid tumor type. The result and conclusion of the majority (94%) of Phase I trials was to establish a RP2D for future studies and this has not significantly changed over time.

A vital piece of information for any reader of a clinical trials paper is the identification of the trial sponsor and this information was missing or not clear in almost 30% of papers. However, reporting of sponsorship has improved in the last decade with an apparent increase in commercial industry sponsorship 5 versus 80% academic sponsor (15% still not clearly provided). Figure 1 graphically displays some of the abovementioned trends. Despite these changes in childhood cancer Phase I trial design, the average number of patients entered (mean 29.9 vs 26.8) and evaluated (mean 26.8 vs 24.1) has remained stable between the most recent decade and the preceding one (Table 2). The age range of patients enrolled and the number of dose levels studied (median of 4, range of 2–13) appears unchanged with time.

The duration of published Phase I studies could be calculated when the start and completion dates were given in the paper (only 76 provided this data out 126). The duration of the Phase I trials were similar whether conducted in the first or second decades and also did not appear to differ in terms of study duration between conventional cytotoxic or targeted agents. Although only a small number of trials studied biologics, such as differentiating agents (e.g. cis-retinoic acid) or immune-modulating agents (e.g. IFN), these appeared to take longer to complete, with a median 4.5 years. Of interest, Phase I studies with a dose expansion cohort

Table 1. Main features of Phase I studies by decade of publication.

		Total n (%)	1993–2003, n (%)	2004–2013, n (%)	p-value†
Number of published Phase I studies identified		126	51 (40.48)	75 (59.52)	N/A
Number of different agents		90	35	60	N/A
Type of study	Phase I	108 (85.71)	49 (96.08)	59 (78.67)	0.012
	Phase I + expansion cohort	8 (6.35)	0 (0)	8 (10.67)	
	Phase I/II	10 (7.94)	2 (3.92)	8 (10.67)	
Type of Phase I design	3 + 3	91 (73.39)	35 (71.43)	56 (74.67)	0.007
	CRM	7 (5.65)	0 (0.00)	7 (9.33)	
	Rolling 6	3 (2.42)	0 (0.00)	3 (4.00)	
	Other	23 (18.55)	14 (28.57)	9 (12.00)	
Type of administration	Oral	45 (35.71)	9 (17.65)	36 (48.00)	0.001
	IV	75 (59.52)	40 (78.43)	35 (46.67)	
	Other	6 (4.76)	2 (3.92)	4 (5.33)	
Mechanism of action	Cytotoxic	65 (51.59)	39 (76.47)	26 (34.67)	<0.0001
	Targeted therapy	46 (36.51)	4 (7.84)	42 (56.00)	
	Biologics‡	15 (11.90)	8 (15.69)	7 (9.33)	
Phase I study population	Solid tumors	30 (23.81)	10 (19.61)	20 (26.67)	0.144
	CNS	28 (22.22)	8 (15.69)	20 (26.67)	
	Mixed	68 (53.97)	33(64.71)	35 (46.67)	
Phase I recommendation	RP2D	34 (26.98)	16 (31.37)	18 (24.00)	0.525
	RP2D + Phase II suggested	57 (45.24)	20 (39.22)	37 (49.33)	
	RP2D + Phase II ongoing	26 (20.63)	10 (19.61)	16 (21.33)	
	No RP2D	6 (4.76)	4 (7.84)	2 (2.67)	
	Other	3 (2.38)	1 (1.96)	2 (2.67)	
Type of sponsor	Academic	85 (67.46)	25 (49.02)	60 (80.00)	<0.0001
	Pharmaceutical	4 (3.17)	0 (0)	4 (5.33)	
	Not available	37 (29.37)	26 (50.98)	14.67)	

†p-values for the Fisher's exact test of association.
‡Biologics = differentiating agents, immune-modulating agents. Cellular-based therapies were excluded.
CNS: Central nervous system tumor; CRM: Continuous reassessment method; IV: Intravenous; n: Number; RP2D: Recommended Phase II dose.

or an integral follow on Phase II component did not take appreciably longer than those with only a dose escalation Phase I design (mean 2.5, 3.1 and 2.6 years, respectively), and there was a trend to a shorter duration with CRM and the 'rolling 6' (Table 3).

There were 83 (65.9%) Phase II studies that corresponded to one of the original 126 Phase I trials, and there was no substantial difference in terms of the likelihood of a corresponding Phase II for the two time periods (36 out of a total of 51 [70.6%] in 1993–2003 vs 47 of 75 [62.7%] in 2004–2013). However, Phase I trials involving cytotoxic agents were more likely to have a subsequent Phase II study (48 of 65, 73.9%) compared with Phase I studies investigating targeted agents (25 of 46, 54.4%). On the whole, only 39 pairs of correlated Phase I and Phase II studies provided enough information to allow a calculation of the time interval between the Phase I and the Phase II (Figure 2). Overall the mean time interval between a Phase I study and its corresponding Phase II was 3.5 years (range 1–18 years); however, it does appear that the interval has decreased in the most recent decade (mean 2.4, range 1–7 years) compared

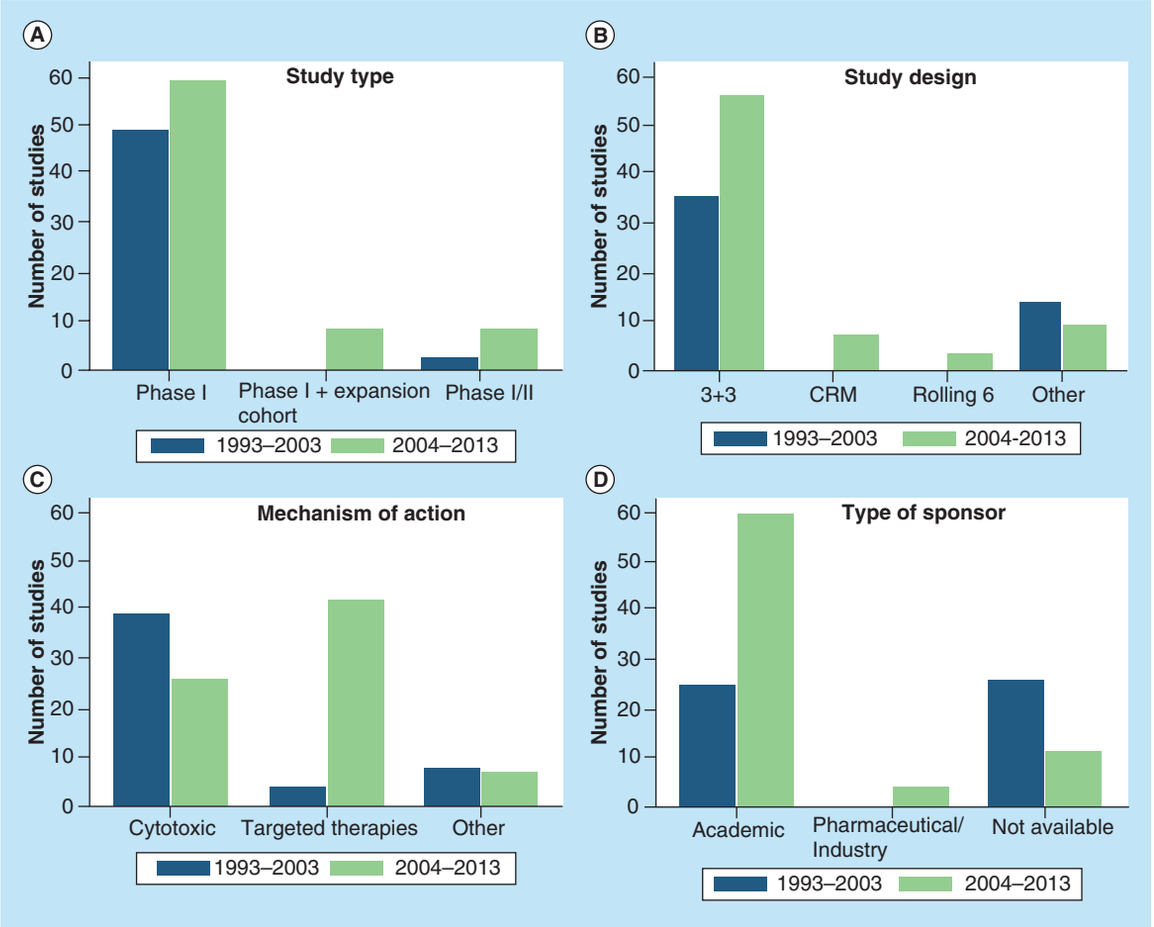

Figure 1. Phase I studies characteristics by decade of publication.
CRM: Continuous reassessment method.

with the preceding decade (5.3, range 1–18 years). Although it must be recognized that Phase I studies only recently completed and reported would be less likely to have a corresponding Phase II study due to the short follow-up and this could influence the results. For the 39 studies with a start and end date for completed Phase I and a start date for the corresponding Phase II study, Figure 3 graphically demonstrates in chronological order the time taken to complete the Phase I and the time interval to the corresponding Phase II.

Table 2. Participants characteristics by decade of publication.

		Total	1993–2003	2004–2013
Average number of patients entered	Mean (SD)	28.67 (13.42)	26.84 (13.36)	29.91 (13.42)
	Median (range)	25 (5–71)	23 (10–71)	26 (5–68)
Average number of patients evaluated	Mean (SD)	25.74 (13.31)	24.06 (12.55)	26.88 (13.77)
	Median (range)	22 (5–91)	21 (9–71)	23 (5–91)
Participants' minimum age (yr)	Mean (SD)	2.62 (1.62)	2.34 (1.32)	2.81 (1.78)
	Median (range)	2 (0–11)	2 (0–7)	3 (0–11)
Participants' maximum age (yr)	Mean (SD)	19.77 (4.93)	20 (7.15)	19.62 (2.58)
	Median (range)	20 (10–63)	20 (10–63)	20 (13–29)
Dose levels evaluated	Mean (SD)	4.63 (2.10)	4.51 (2.10)	4.72 (2.11)
	Median (range)	4 (2–13)	4 (2–13)	4 (2–10)

SD: Standard deviation; Yr: Year.

Table 3. Duration of Phase I studies by decade, study type, study design and mechanism of action.

	Mean (yr)	SD	Median (yr)	Range (yr)	n
Decade					
1993–2003	2.59	1.45	3	0–6	29
2004–2013	2.72	1.35	3	1–6	47
Study type					
Phase I	2.63	1.39	3	0–6	63
Phase I + expansion cohort	2.50	1.05	2.5	1–4	6
Phase I/II	3.14	1.57	3	1–6	7
Study design					
3 + 3	2.61	1.33	3	0–6	59
CRM	2.40	0.89	3	1–3	5
Rolling 6	2.00	1.00	2	1–3	3
Other	3.25	1.91	3	1–3	8
Mechanism of action					
Cytotoxic	2.52	1.35	3	0–6	42
Targeted therapy	2.35	0.98	2	1–4	26
Biologics†	4.50	1.41	4.5	3–6	8
Total	2.67	1.38	3	0–6	76

†Biologics = differentiating agents, immune-modulating agents.
CRM: Continuous reassessment method; n: Number; SD: Standard Deviation; Yr: Year.

Discussion

Optimization of early phase clinical trials efficiency will better facilitate the introduction of novel therapies in childhood cancer. Our analysis of Phase I trials over two decades shows an increase in the number of Phase I trials and the number of new agents studied with a notable change from conventional cytotoxic chemotherapy to biologically targeted anticancer agents. However, the increase is modest and disappointing when considered in the context of the explosion in knowledge and understanding of the biology of cancer and resulting availability of new targeted anticancer agents. Despite the introduction of new regulations and incentives by both the FDA and the European Medicines Agency (EMA) there remain considerable challenges with regard to access to novel agents for children with cancer, as the new regulations have not led to the expected increase in industry or academic sponsored early phase clinical trials. The on-going discussions and possible solutions have been extensively discussed and reported in several recent papers, including a 'mechanism of action' rather than tumor specific basis for requiring pediatric investigation [8–13]. One particular concern is how to deal with a novel agent that is not taken forward due to lack of activity in adult cancer but which has shown activity in a childhood cancer, for example, Ewing sarcoma and IGF-1R signaling and this will require partnership between industry, regulators and the academic community to resolve [14–18]. The change from intravenous to oral agents may initially appear beneficial for patients, but actually presents a challenge for the conduct of pediatric oncology trials. If there is no suitable pediatric formulation available and with only adult size and dose capsules/tablets, it may be difficult for administration in young children and make appropriate dose escalation difficult.

Our analysis did reveal that some Phase I trial design changes have occurred, such as the introduction of newer dose escalation methodologies such as the CRM or 'rolling 6' designs that aim to improve the efficiency of Phase I studies compared with the classical 3 + 3 design [19–21]. However, there has been no subsequent reduction in the number of patients or the duration required to complete a Phase I study, with a median of 2–3 years. This could be due to either the limited introduction of these newer methods or the fact that some have questioned as to how efficient the CRM and rolling 6 methods are compared with the classical 3 + 3 [22,23]. The number of dose levels required has also not changed with the median remaining at 4, this is somewhat surprising in view of the move to more targeted therapies were there may not be a need to continue to dose escalate to a maximum tolerated

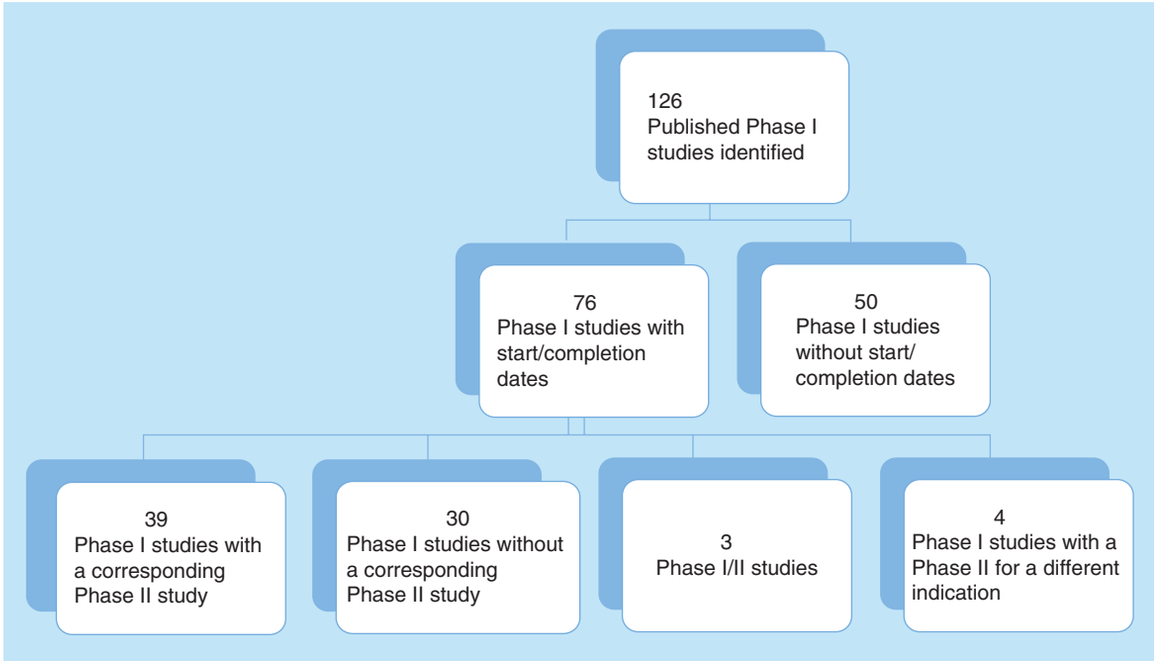

Figure 2. Flow diagram of Phase I and Phase II studies selection for assessment of Phase I to II time-interval evaluation.

dose (MTD) as an optimum biological dose (OBD) may be achieved prior to dose-limiting toxicities.

There also has been a move to include dose expansion cohorts within Phase I trials with the aim of enrolling more patients at the RP2D to provide the opportunity of gaining more pharmacokinetic, pharmacodynamic analyses, as well as preliminary tumor response data, this has mirrored a trend in adult oncology practice [24]. A few trials have been designed to have an integrated statistically powered Phase II study embedded following the dose escalation phase. Of interest these combined Phase I/II trials did not take appreciably longer to accrue and as a result this seamless integrated design reduced the time interval to start a Phase II study compared with the mean time interval of 2.4 years with separate Phase I and II studies, a significant increase in efficiency.

Although the majority (94%) of the 126 Phase I studies established a RP2D for a future Phase II study, only 83/126 (65.9%) had a corresponding Phase II identified. The reasons as to why almost 30% of agents did not move forward to a Phase II study when this was recommended are not known but the data showed only 54.4% of targeted agents had a corresponding Phase II compared with 73.9% of cytotoxic agents. One possible explanation is the fact that some Phase II trials have not been registered or their results published, or in some instances, the start dates are not available, particularly for those conducted in the earlier years. This is a limitation inherent to the methodology employed, but we would expect the number of such cases to be rather small and have minimal impact in our results. Another possibility is that this may simply reflect a shorter follow-up for targeted agents Phase I studies but raises concerns that investigators have difficulty in securing further access from industry for these experimental therapies prior to critical adult cancer market authorizations and widespread availability within the adult oncology market. However, when access to these agents is available the time intervals between Phase I and II studies has decreased, obviously this is a positive trend that needs to be encouraged.

One point of concern we found during our searches and analysis was the in consistency of reporting of vital information with regard to study conduct. In 30% of Phase I study papers it was not clear who was the study sponsor and we regard this as a vital piece of information for the reader and reviewer. In almost 40% of studies the report did not give study start and completion dates or an indication of whether the study recruited to target. It would appear that a standardized way of reporting early clinical trials with a checklist of critical basic information would be useful for journal to request much in the same way as the CONSORT guidelines for randomized clinical trials [25].

Conclusion & future perspective

The need for the rapid and efficient investigation and introduction of novel agents for childhood cancer is incontrovertible. However, our analysis has

demonstrated only modest changes in early phase trial design of the last two decades despite previous papers indicating that newer Phase I trial designs could improve efficiency [26,27]. Pediatric studies are rarely if ever conducted without knowledge from adult cancer trials of toxicity profiles, pharmacokinetic and in many cases relevant pharmacodynamic data with an RP2D for the adult population. Previous studies have demonstrated that there is a tight correlation between the adult RP2D and the MTD of the same agent in children [26]. It has previously been recommended that the starting dose for a pediatric Phase I study should be 80% of the adult MTD to avoid unnecessary exposure to low ineffectual doses [3]. In the era of targeted medicine it could be argued that an appropriate pediatric starting dose should be the 100% equivalent of the adult dose with a dose-1 cohort level available if significant toxicity occurred at this first level. The incorporation of appropriate biomarkers to measure the expected pharmacodynamic effects of the agent as validated in prior adult studies should allow an optimum biological dose to be determined and mean that titrating to significant toxicity and establishing an MTD may not be required and reduce the number of dose cohorts studied. This would allow a reduction in the time and number of patients required in the dose escalation phase and lead to a more rapid move to a dose expansion phase or preferably a formally powered and embedded Phase II study of defined populations. The initial phase would become a 'proof-of-mechanism' study in which the biologically targeted agent was demonstrated to hit the target at an OBD in childhood tumors confirmed

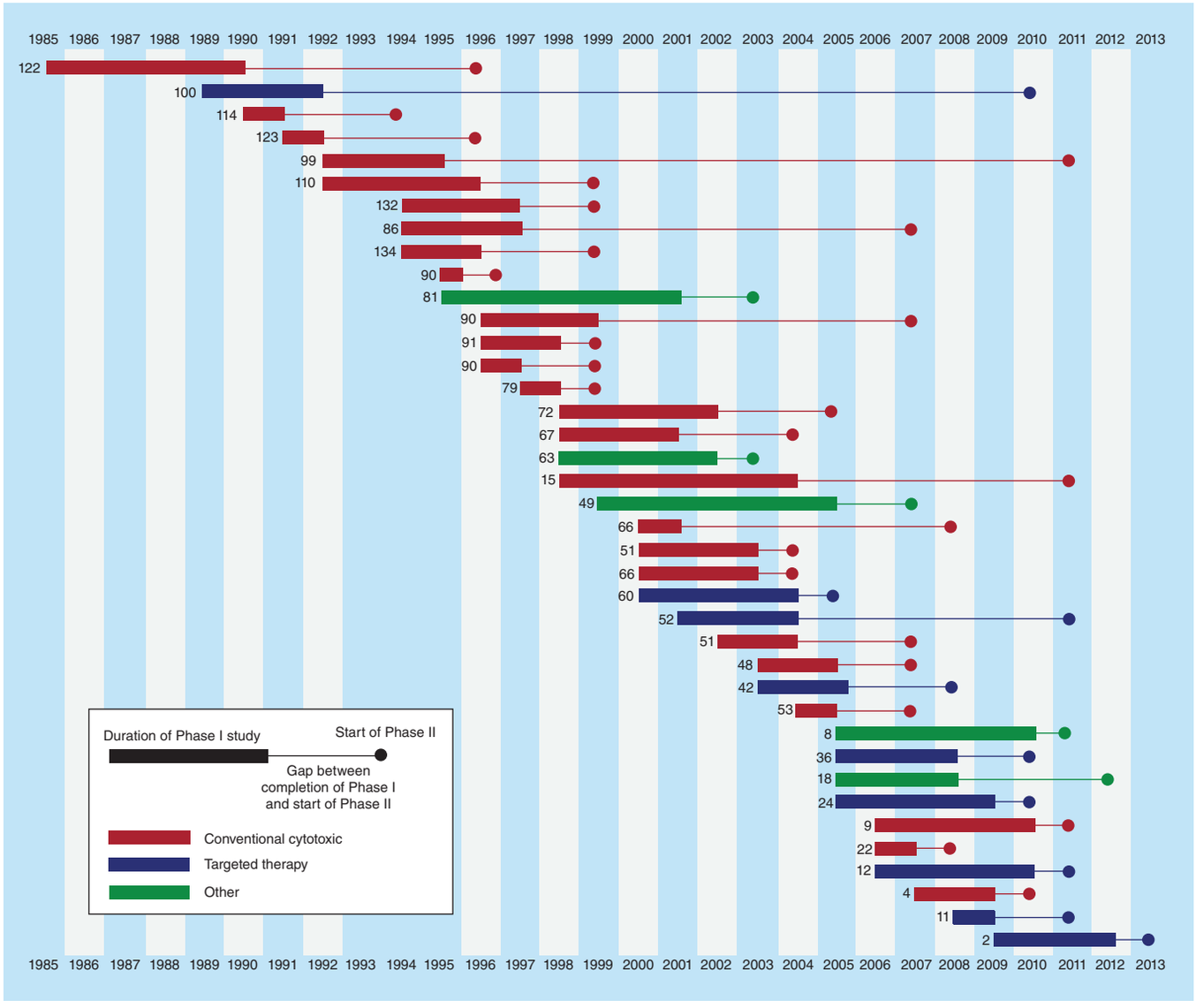

Figure 3. Phase I to II time interval by year of publication and mechanism of action of agent investigated.

by an appropriate biomarker. The inclusion of tumor biopsy at the time of relapse (to avoid bias from tumor evolution which may occur if only archival diagnostic samples are used) and even serial biopsies pre and post study drug exposure is increasingly common in adult Phase I trials. There are certainly additional ethical concerns in children; however, if supported by relevant adult clinical and relevant preclinical data, either direct tumor biopsy or a validated surrogate biomarker can and have been successfully employed in pediatric trials following appropriate ethical, safety and assent/consent consideration. Having proved that the proposed mechanism of action is achievable at the OBD the integrated dose expansion/Phase II element would then become a 'proof of concept' study to establish if a predetermined direct clinical benefit in a given population (may be a tumor type or presence of a target, e.g., actionable mutation) can be demonstrated (i.e., tumor response or progression-free survival). This proof-of-concept phase could even allow for a randomization against an appropriate control arm to be studied. Such a seamless integrated design would allow one study to provide sufficient data to allow a critical 'go/no go' decision to be made as to whether to take forward into a formal efficacy Phase III study. This would improve efficiency with only one set of regulatory approvals required, no downtime between Phase I and Phase II trials, less patients required and likely less cost. This could also be adapted to allow a more rapid study of possible novel therapy combinations, with these occurring within the context of one trial if supported from previous preclinical and adult data. This could then be followed by a multi-arm Phase II integrated study to compare single versus combination therapy. Hopefully, this combined Phase I/II development would also be more likely to secure continued access for the novel therapy from industry, as negotiations would be centered at one time point for one trial only and reduce any external negative influences from adult market considerations.

It remains vital that academics, regulators and industry working with patients and family representatives continue to refine the current legislation and incentive schemes to gain better access to new therapies for children with cancer. However, it is essential that efficient trial designs be introduced to maximize efficiency and speed up the introduction of effective agents into standard clinical practice in pediatric oncology.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at www.future-science.com/doi/full/10.4155/cli.14.105.

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Executive summary

- Urgent need for novel therapies in childhood cancer to improve survival and introduce less toxic treatments to reduce the burden of therapy.
- Increased understanding of the molecular biology of childhood cancer has identified new targets and corresponding biologically targeted therapies are increasingly available.
- New early clinical trial methodologies incorporating biomarkers to assist in appropriate patient selection and pharmacodynamic evaluation have been adopted in adult oncology practice aiming to improve the efficiency of the drug development process.
- Despite new regulatory frameworks in US and Europe there has been only a modest increase in the number of Phase I trials over the past two decades.
- To promote more industry and academic early phase trials there needs to be on-going discussions, with consideration of possible changes in the regulations, for example, mechanism of action based rather than specific tumor indications.
- Limited adoption of new methodologies has not significantly improved the efficiency of early phase clinical trials in childhood cancer in terms of number of patients and dose cohorts required to complete standard Phase I studies.
- Despite the establishment of a recommended Phase II dose and schedule being available up to 30% of agents do not progress to Phase II studies.
- The time interval from the completion of a Phase I study to the opening of a Phase II trial has improved over the past two decades but still has a mean time interval of 2.4 years.
- Prior information is available from adult studies for the majority if not all novel agents and by better modeling of this available data (dose, schedule, pharmacokinetic and pharmacodynamic) more efficient early clinical trial design could reduce the number of patients and dose levels required in the pediatric dose finding phase.
- A move to more integrated combined Phase I/II studies with sequential 'proof of mechanism' and 'proof of concept' phases may provide a seamless and quicker early drug development process to allow a more efficient introduction of novel therapies into standard of care in childhood cancer.

Financial & competing interests disclosure

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