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European collaboration in trials of new agents for children with cancer

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Abstract

Childhood cancer is a relatively rare disease, representing just 1% of all malignancies. Within Europe, this represents some 12,000 new cases each year, with approximately 1600 a year in the United Kingdom and 1800 in France. International collaboration in phase III trials of childhood cancer has been the norm for many years, traditionally within Europe, but, largely because of organisational considerations, phase I and II trials have only been conducted on a national basis. With overall cure rates in the region of 70%, relatively few children are available for these early drug trials. Access to new drugs is also a major problem. Against this background, a United Kingdom (UK)/French 'new agent' collaboration was established, expanding subsequently into a wider European grouping. This paper documents the history of that collaboration, the outcomes and future challenges.

Keywords: Childhood cancer; International collaboration; Phase I/II studies; New agents

1. Introduction

Childhood cancer is a relatively rare disease, representing just 1% of all malignancies. In Europe, this amounts to some 12,000 new cases each year, with approximately 1600 a year in the United Kingdom (UK) and 1800 in France. When broken down into individual tumour types, the numbers, even for the commoner childhood tumours, are often too small to ensure that clinical trials can be completed satisfactorily at a national level. It is for this reason that the majority of phase III trials of childhood cancer have, for some years now, been conducted on an international and collaborative basis. While adding to the complexity in terms of clinical discussion and compromise, as well as practically, organisationally, and financially, this has meant that more randomised trials can be conducted.

Traditionally within Europe, and largely because of organisational considerations, phase I and II trials have tended to be conducted on a national basis. With overall cure rates for children with cancer currently in the region of 70%, relatively few children are eligible for entry to these 'early' drug trials. Recruitment to trials may therefore be slow. However, rather than problems with recruitment, the real dilemma facing paediatric oncologists is that few 'new' agents are offered for investigation in children.

Many of the chemotherapy drugs now in use for the treatment of children with cancer have been available for many years. Access to new drugs is a problem. It is generally accepted, for ethical reasons, that new drugs must first have gone through trials in adults before being given to children. However, most drugs studied in adults are never subsequently offered for investigation in

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children in Europe despite the fact that many hundreds of compounds are currently under investigation [1]. Paediatric oncology represents only a small market for an approved drug compared with common adult cancers such as breast or lung cancer. Paediatric studies are not usually part of licensing applications. The commercial interest to the pharmaceutical industry is, therefore, extremely limited. Of 217 medicinal products granted, a European Community marketing authorisation (status October 2002), 25 were authorised for the diagnosis or treatment of a malignancy or cancer-related condition (Ref. European Medicines Evaluation Agency web site), but only two of them had been evaluated in children prior to submission. In 1999, the first of these two agents – Temodal® (temozolomide) – was licensed for the treatment of patients with recurrent glioma. The Summary of Product Characteristics indicated use in patients 3 years of age or older, on the basis of a paediatric phase I study run within the United Kingdom Children's Cancer Study Group (UKCCSG) New Agents Group [2]. In 2001, the second drug – Fasturtec® (rasburicase) – was indicated for the treatment of tumour-induced hyperuricaemia, with pharmacokinetic evaluation in children and adolescents. It is not unknown for a drug with potential promise in children to be dropped by the company because of a lack of activity in adults, even though considerable time may already have been spent in discussions and paediatric protocol development.

2. Establishment of a joint French/UK collaboration

Against this background, the New Agents Group of the UKCCSG and the Pharmacology Group of the Société Française d'oncologie Pédiatrique – SFOP, came together formally in mid-1995 as NAG/SFOP, to discuss possible collaboration and the conduct of joint studies. Past and current phase I and II trials activity [3] for each of the national groups were reviewed, as well as structure, membership, funding and organisation, any existing relationships with the pharmaceutical industry, as well as any potential obstacles to collaboration.

The two groups differed in structure. In the UK, the New Agents Group had been formed in 1987 with the aim of providing a mechanism for investigation of new agents in children's tumours within the multidisciplinary structure of the UKCCSG. The group has specific criteria for centres wishing to participate in phase I and phase II trials. These are more stringent for the phase I trials. The key requirement is the need for a committed clinician in the centre, a research nurse, and the capacity to meet the urgent reporting requirements. The research nurses complete the Case Report Forms (CRFs), also organise and carry out many of the practical tests, administer treatment and offer support, and discuss the trial with the patients and/or their families. Twelve of the 22 UKCCSG centres currently fulfil the phase I criteria (Table 1), although not all are represented on the New Agents Group. Coordination of all of UKCCSG activities is through the Data Centre in Leicester.

In France, the SFOP comprises of 33 paediatric oncology centres. The aims of the Society include conducting clinical research for children with malignant solid tumours, but not leukaemia. A phase II committee had been created in 1986. In 1994, this developed into the Pharmacology Group (GP), aiming at conducting phase I and phase II studies, pharmacology studies and improving methodology. The GP-SFOP comprises eight centres (Table 1) which have government agreement to perform studies without direct individual benefit, according to the French law for Good Clinical Practice (GCP) and conform to written SFOP criteria. These eight centres manage 60–70% of all new cases of solid tumours diagnosed in France each year. There is no centralised trials unit. This task is performed by a few larger institutions such as the Institut Gustave Roussy, the Institut Curie and the Centre Léon Bérard. In France, Clinical Research Associates complete the CRFs, which are then validated by the referring

Table 1
Phase I clinical centres in GP-SFOP and UKCCSG

GP-SFOP centre	Lead clinician	UKCCSG centre	Lead clinician
Institut Curie, Paris	Dr. François Doz	Birmingham Children's Hospital	Dr. Bruce Morland
Institut Gustave Roussy, Villejuif	Prof. Gilles Vassal	Royal Hospital for Sick Children, Bristol	Dr. Steve Lowis
Centre Oscar Lambret, Lille	Dr. Fabienne Pichon	Addenbrooke's Hospital, Cambridge	Dr. Denise Williams
Centre Léon Bérard, Lyon	Dr. Didier Frappaz	Yorkhill Hospital, Glasgow	Dr. Milind Ronghe
Hôpital de La Timone, Marseille	Dr. Jean-Claude Gentet	Great Ormond Street Hospital, London	Dr. Julia Chisholm
Hôpital d'Enfants, Nancy	Prof. Pascal Chastagner	St. James's Hospital, Leeds	Dr. Ian Lewis
CHU Purpan, Toulouse	Dr. Hervé Rubie	Alder Hey Hospital, Liverpool	Dr. Heather McDowell
Hôpital Trousseau, Paris	Prof. Judith Landman-Parker	Royal Manchester Children's Hospital	Dr. Eddy Estlin
		Queens Medical Centre, Nottingham	Dr. David Walker
		Royal Victoria Infirmary, Newcastle	Prof. Andrew Pearson
		Royal Marsden Hospital, Sutton	Prof. Ross Pinkerton
		Southampton General Hospital	Dr. Jan Kohler

clinicians. All contact with family and patients is carried out by physicians.

From the outset, there was a strong commitment to share ideas and work together, particularly in the planning of joint trials. This collaboration was based on a common therapeutic philosophy, shared interests in drug development and pharmacology, and recognition of the importance of ensuring optimal use of the available patient population for early drug clinical trials.

3. New drug development activity – between 1994 and 2002

From January 1994 to September 2002, the two groups have evaluated 10 different drugs within 17 studies, of which 13 are closed, 3 are ongoing and 1 is suspended. This represents 559 study participations with 64% of them in France and 36% in the UK. There were nine phase I trials (dose-escalation), six phase II trials and two pharmacokinetic studies. Details are provided in Fig. 1. A pharmacokinetic/pharmacodynamic evaluation was performed in all but three of the studies.

Of the 10 drugs evaluated, nine were 'classical' cytotoxic agents, one was a multi-drug resistance modulator and eight were new to the treatment of paediatric tumours. Two 'old' drugs, namely thiotepa and carboplatin, were explored at high-dose and/or studied at the pharmacokinetic level. Only 4 of the 10 drugs, namely temozolomide [2], PSC833 [4], AG337 [5] and Busulfex, were studied before any European registration in adult cancer. Four compounds, new for the treatment of paediatric malignancies, namely CPT-11 (irinotecan) [6], DaunoXome [7], Taxol (padetaxel) [8] and oxaliplatin [9], were available after approval for use in adult cancer patients.

A median number of eight centres (range 3–24) participated in the studies. The median number of patients registered in each study was 28, ranging from 12 (area under the concentration curve (AUC)-escalation study of high-dose carboplatin) to 81(phase I study of CPT-11). The median duration of the closed studies was 28 months, ranging from 9 months (phase I study of padetaxel) to 44 months (phase I study of CPT-11). Over this 7 year 9 month period, the estimated accrual rate to open studies was one patient in phase I and one patient in phase II studies per month. The number of inclusions per year was directly related to the number of studies open, ranging from 22 inclusions in two studies in 1994 up to 79 inclusions in eight studies in 2001. Indeed, new drug development activity was limited by the number of drugs available rather than by the patient accrual potential.

4. Collaborative studies

During the period, four joint studies were conducted by the two groups. The first was a phase I dose-escalation study of the multi-drug resistance modulator PSC833 (an analogue of cyclosporin A) in combination with etoposide in relapsed patients with relapsing and/or refractory solid tumours [4]. The second, following successful completion of the phase I study in the UK [10], was an extended phase I (effectively a phase II) study of temozolomide in patients with Brain Stem Glioma or High

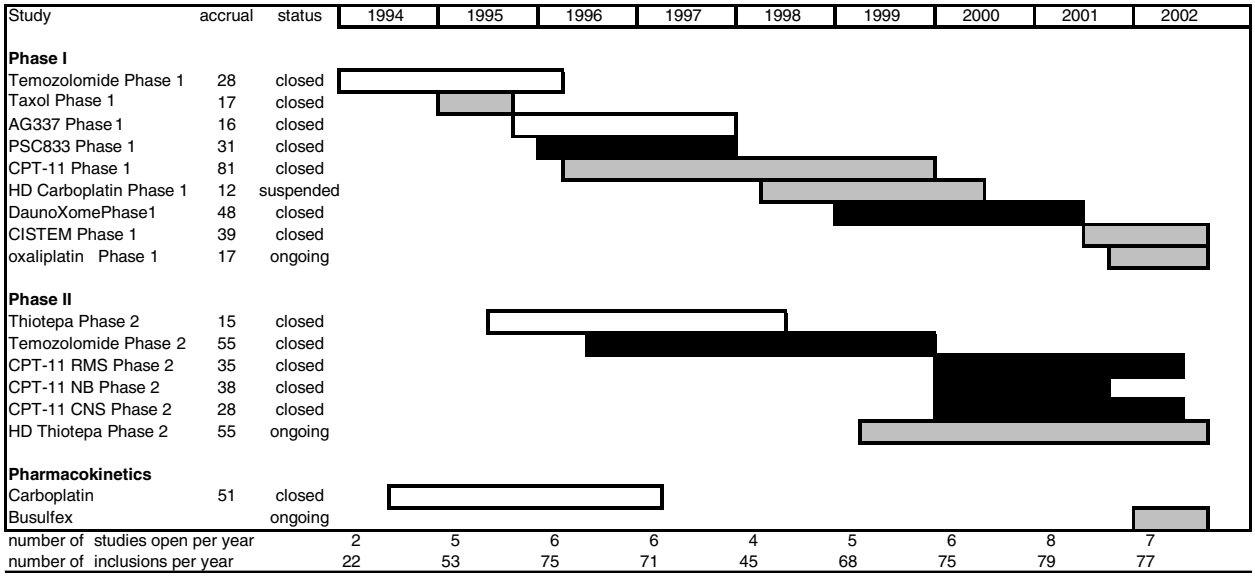

Fig. 1. Phase I and phase II study activity from January 1994 to September 2002. Studies were conducted in the United Kingdom (UK) (white), in France (grey) or in both countries (black). CISTEM, cisplatin and temozolomide combination; RMS, rhabdomyosarcoma; NB, neuroblastoma; CNS, central nervous system; HD, high dose; Taxol, Padetaxel; CPT-11, irinotecan; DaunoXome; Liposomal daunorubicin.

Grade Glioma. This study opened in January 1994, as a phase I study in the UK, and closed to recruitment in February 2000. It recruited 55 children with either relapsed World Health Organisation (WHO) grade III–IV high grade gliomas (34 patients) or diffuse intrinsic brain stem gliomas progressing after standard radiotherapy (21 patients). Only 81% were ultimately found to be eligible for the trial after common histological and radiological review. This highlighted the difficulties experienced by neuropathologists, and the national bias in distinguishing malignant astrocytes from oligodendrocytes, and otherwise 'unclassifiable' cells. This study also served as a basis for suggesting common radiological guidelines for assessment of response in paediatric brain tumours [14].

A joint phase I study of DaunoXome (liposomal daunorubicin) opened in December 1998 and closed in June 2001 [7]. The study contained two arms, one for patients who had been heavily pre-treated and the other for those who had not. This study recruited quickly, with 153 patients pre-registered and a total of 48 patients entered over 31 months. However, it did illustrate the difficulties of managing dose-escalation when a large number of participating centres were involved. The French group and parents, in particular, did not feel comfortable with the concept of a waiting list and, undoubtedly, some patients did become ineligible while on the waiting list. The future of this drug is, at the moment, uncertain as the cardiotoxicity encountered in this study may preclude it from further development in children.

The GP-SFOP conducted a phase I study of CPT-11 given once every 3 weeks in two cohorts of patients. A total of 81 patients in three centres were recruited to this study, which identified a much higher recommended dose (600 mg/m^2) than that found in adult phase I studies [6]. A joint phase II study was then launched in December 1999 and completed in June 2002 with 101 patients in three tumour groups: neuroblastoma [11], rhabdomyosarcoma [12], and medulloblastoma/primitive neuroectodomal tumour (PNET) [13]. This study evaluated prospectively the pharmacokinetic/pharmacodynamic relationship of this highly metabolised drug, using a limited sampling strategy set-up using the phase I pharmacokinetic data. In addition, the influence of gene polymorphisms was evaluated. Recruitment was relatively slow with a marked difference between the UK and France (18 in the UK compared with 83 in France). There is a clear need to shorten the duration of phase II studies by improving recruitment rates.

Two new joint studies opened in 2003 – a phase II study of temozolomide for relapsed neuroblastoma patients and a phase II study of Glivec (STI 571, imatinib mesylate).

During the same period, contacts have been established with North American groups involved in new drug development in children with cancer. A consensus document for Europe and North America [3] for phase I trials has been established. Meetings are held each year to share experiences and avoid competing studies. Ultimately, it is hoped that joint collaborative studies will be undertaken.

5. Reflections on achievements to date

This Anglo-French collaboration has raised a number of issues including: (a) pathology and radiology review, including differences of definition; (b) haematological end-points; and (c) response assessment. Initial differences in methods for tumour assessment by UK and French neuroradiologists have been resolved, resulting in publication of neuro-radiology imaging guidelines [14], now routinely incorporated in contemporary brain tumour protocols. Another challenge has been working within a period of rapid change in the conduct of clinical trials, with the introduction of GCP and the European Union (EU) Directive on Clinical Trials (2001/20/EC), the full implications of which are not yet clear.

The scarcity of the patient population, the relative lack of new agents for study, and the issue of slow recruitment have all raised questions of study methodology. In particular, the Group has debated the question of whether conventional dose-escalation schedules should still be used in phase I studies of children or whether to adopt new methods of study design, such as the Continuous Reassessment Method (CRM) [15] which, in theory, requires less patients to reach the desired end-point. The CRM is currently in use in a phase I SFOP study of cisplatin and temozolomide [16]. This methodology may allow better consideration of some covariates such as previous treatment ('heavy' or not) in dose-escalation and thus avoid performing two parallel studies in two separate cohorts. Further work is required in the area of phase I methodology. There is also a need to shorten the time for completion of phase II studies, possibly by the inclusion of more centres.

While this collaboration has been successful, not least in overcoming the logistics of conducting these trials on a multi-national basis, there are a number of issues to be considered. Although a total of 17 studies have been commenced in the past 7 years of the NAG/SFOP collaboration, only four joint studies have been completed. It is not clear whether this is a reflection of a problem with the organisation, with drug availability, of patient numbers, with the pharmaceutical industry, or with a variable combination of these factors.

Other national groups or centres expressed an interest in joining NAG/SFOP. In November 2001, therefore, EURONAG – a federation of national groups dedicated

to the development of new agents and pharmacological studies – was formed with the inclusion of centres in The Netherlands and Germany. Italy joined in the autumn of 2002. Widening the original collaboration has several advantages, including an increased patient pool, increased clinical and scientific expertise and, potentially, increased access to new agents. A number of potential hurdles – increased complexity of organisation, funding requirements, and possibly ethical and legal issues – will have to be overcome in order to expand participation in joint studies. The new phase II study of imatinib mesylate, which opened late in 2003, is the first to be undertaken within the broader framework of EURONAG.

6. Challenges for the next 10 years

A large number of new compounds with novel mechanisms of action are being developed in oncology in adults. Moreover, high-throughput technologies for the analysis of gene expression provide new opportunities to identify potential therapeutic targets and to develop more specifically targeted drugs than conventional cytotoxic agents. This raises a number of issues in terms of drug discovery and methodology for drug development, since most of these agents are not expected to be used and active at the identified maximum tolerated dose. A major challenge for paediatric oncology is to gain access to these new agents for children with incurable or recurrent cancers. This is a critical issue and a public health problem at the European level.

Generally, the drugs available for paediatric development are only those with demonstrated activity in adult cancers. There are many examples of cytotoxic drugs tested to phase II in adults, demonstrating little or no response, which are never taken forward to the market place. Children have different tumours to adults and in general they are much more chemosensitive. We do not know whether any of the cytotoxic drugs, lost because of a lack of adult activity, may have been active agents in children. Thus, paediatric studies on anticancer compounds should not be conditional on the demonstration of activity in adult patients.

In terms of the drug 'pipeline', the main route is through the pharmaceutical industry and more than 90% of anticancer drugs that should be evaluated in children within the next 10 years are expected to come from big pharmaceutical companies or start-ups. Another challenge, therefore, is how to incite the pharmaceutical industry to evaluate their drugs in children before they seek approval in adults.

Some anticancer agents, in particular, those aimed at a specific molecular target in a paediatric tumour type, for example, the EWS-FLI translocation product in Ewing's tumour, will come through academia, or through organisations such as Cancer Research UK. It will be almost impossible in the future for academic institutions to take forward promising new therapeutics without the support of industry. The additional cost of producing medicinal agents to Good Manufacturing Practice (GMP), and conducting clinical trials to GCP standards can be prohibitively expensive. As a consequence, less than 10% of new anticancer compounds likely to be studied in children will come through non-industrial organisations.

Major changes are being made in the regulatory environment to encourage new drug development for children with cancer. The Orphan Drug Act was launched in 2000 in Europe and offers advantages for the development of new drugs in rare diseases, such as paediatric malignancies. In addition, there are financial incentives to the pharmaceutical industry to take forward promising new drugs in paediatrics (not exclusively oncology). In the United States of America, the "Pediatric Rule" recognised the importance of properly evaluated drugs for children and promotes paediatric studies during all new product development programmes [17]. Subsequent legislation in the US – "Pediatric Exclusivity" and "Best Pharmaceuticals for Children Act" – have laid the foundations for financial incentives to industry for performing paediatric studies. These regulations have been successful in the US [18] and Europe is currently developing a Paediatric Medicine Regulation (expected in 2005) that will provide incentives to pharmaceutical companies which will promote evaluation of their compounds in children.

It is unlikely that new breakthroughs in paediatric oncology will be in non-specific cytotoxic therapy. Instead, current research activity focusses more on tumour-specific targets, some of which will be common to adult and childhood cancers, and others unique to paediatric tumours. Some compounds may have different targets in cancer cells and are likely to be active in combination with other non-cytotoxic compounds or conventional chemotherapy. The main challenge is to have access to these new compounds for children during the early stages of their development in adult patients. Tumour biology and evaluation of these targets in paediatric tumours will be a key issue to identify those compounds, with potential antitumour activity, that need to be studied in children. The issue of paediatric-specific therapeutics is even more complex, since the very narrow market is unlikely to attract the pharmaceutical industry because of poor financial returns.

There is a real concern, therefore, that targeted paediatric cancer development will effectively be halted. However, with effective collaboration between scientific groups, clinicians, the pharmaceutical industry and regulatory authorities, it should be possible to keep new drug development for children with cancer on the agenda.

7. The ITCC European Project

It was against this background, therefore, in early 2002, that the concept of the ITCC Project (Innovative Therapies for Children with Cancer) was born. ITCC is an integrated project for new drug development in paediatric oncology that will provide the scientific and clinical communities with a system to enter new generation drugs into the treatment of childhood cancer. The ITCC project comprises researchers, physicians and teams with expertise in paediatric tumour biology and genetics, pharmacology and drug development, and paediatric oncology and early clinical research, along with parents, organisations.

The proposal is to establish an integrated pre-clinical and clinical research framework able to select anticancer compounds requiring paediatric development, to design and conduct high quality mechanistic and therapeutic trials within the specific cultural and clinical needs of member states, and to take into account the unique ethical dimensions of testing new compounds in childhood.

The specific objectives are:

(1) Prioritisation and selection of anticancer compounds being developed by pharmaceutical companies for use in adults that are likely to be active in paediatric cancers, through a comprehensive pre-clinical R&D drug evaluation programme. ITCC has designed a rational mechanism-based strategy for pre-clinical compound prioritisation. This strategy includes: (i) target presence and validation studies in tumours and cell lines representing six paediatric tumour types, responsible for more than 60% of cancer deaths in children, namely neuroblastoma, medulloblastoma, osteosarcoma, Ewing's tumours, rhabdomyosarcomas and acute lymphoblastic leukaemia, (ii) *in vitro* and *in vivo* evaluation of antitumour activity for targeted and non-targeted compounds using relevant paediatric tumour models.

(2) Identification and validation of drug targets unique to paediatric cancers for therapeutic exploitation. This will be followed by identifying the most promising targets to 'hit' followed by optimising agents against this target. Such work will be carried out in collaboration with industry or specialised academic groups, such as the Cancer Research UK.

(3) Demonstration of 'proof of concept' through mechanistic hypothesis-testing phase I/II trials of novel agents, by establishing a clinical trials network with critical mass (numbers of investigator centres and patients) and access to contemporary technologies. New methodology is needed to improve dose-finding studies through a better extrapolation of adult data to the paediatric population.

(4) Working with parents, patients and their representatives to improve access to information and ethical aspects of clinical research in children with life-threatening diseases.

(5) Provision of a training resource to disseminate skills and knowledge of drug testing in childhood malignancies, in order to increase the capacity and capability of the initial and new partners, and to train young scientists and physicians in 'translational' research.

Collaboration with pharmaceutical industry and regulatory bodies will be promoted through ITCC. In addition dissemination of results and strategy through SIOP – Europe tumour committees will assure a coherent and coordinated drug development plan at the European level. It is hoped that funding to take forward this exciting and important venture will be forthcoming as part of the European Framework six programme.

In conclusion, successful collaboration between several European countries of a clinical network for phase I/II clinical trials in paediatric oncology has been achieved. The need to develop future therapeutic agents for childhood cancer is clear. The expansion of the clinical network alongside the integration with drug discovery programmes, including pharma, will be key to meeting the needs of the patients for whom we currently cannot offer curative treatment. Towards this goal, collaboration and partnerships between academic researchers and physicians, parents, pharmaceutical industry and regulatory bodies will be crucial.

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