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Clinical Trials in Paediatric Oncology
Recommendations for the Development of New Anticancer Agents

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Abstract

Childhood and adolescent cancers are rare diseases. Despite the progress in treatment (more than two-thirds of all cases are cured), cancer remains the leading cause of death by disease in children older than 1 year. Access to new drugs that are more efficacious or better tolerated is therefore an important public health priority.

The objective of our round table was thus to take inventory of the situation and to propose recommendations aimed at facilitating coordinated, rational and more rapid access to new treatments. The active participation of paediatric oncologists, parents, pharmaceutical companies and regulatory authorities proved not only necessary but very constructive.

Pharmaceutical companies have developed very few new anticancer agents for children during the past 10 years. The round table identified current trends that appear propitious: the mobilisation of parents and patients' associations; European initiatives to encourage companies to assess drugs in children; regulatory initiatives to guide drug development; and the existence of structured clinical research networks in paediatric oncology, including for the development of early treatment.

The round table recommends the following measures to improve access to new treatments for children and adolescents with cancer:

1. Conduct preclinical paediatric evaluation of all anticancer agents that begin the development process for adults (research and validation of treatment targets; pharmacological evaluation in relevant experimental models) to help choose the agents to study in children.

2. Initiate paediatric clinical development before the first application for authorisation for adults is filed, when sufficient safety and tolerability data are available, that is, after the phase I trials in adults and optimally during the phase II trials.

3. Optimise paediatric clinical evaluation by defining development plans early and by reducing the duration of studies (enlargement of the early treatment research network to ensure adequate recruitment; new evaluation methods; better extrapolation of pharmacological data from adults to children for dose-finding).

4. Improve information to and participation of parents and patients in clinical research for new treatments.

The prerequisite for the success of this project became rapidly clear to all the round-table participants: cooperation and partnership between specialists and other scientists from academia, parent associations, pharmaceutical companies and regulatory authorities. Only with such cooperation can progress in treatment occur and new hopes for recovery be fulfilled.

Keywords: cancer, children, new drugs

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1. Introduction

Despite the important progress in treatment over the past 5 decades, cancer remains the leading cause of death by disease for children older than 1 year. With the treatments used today, full cures occur in only slightly more than two-thirds of all cases. The objective for the next 15 years is therefore more and better cures.

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* Articles, analyses and proposals arising from the Giens Clinical Pharmacology Meetings are the responsibility of their authors and do not reflect the views held by their supervisory organisation.

For that, new drugs must be assessed and therapeutic approaches optimised to diminish the sequelae in adults cured of cancer in childhood.[1]

Although clinical research and treatment in paediatric oncology is well structured and published reports are both numerous and of high quality, new agents become available for development towards registration too rarely. Accordingly, few new anticancer agents have been added to the arsenal of treatments for childhood and adolescent cancers since carboplatin. The objective of this round table was therefore to bring together specialists and other scientists in academia, pharmaceutical companies, parents and regulatory authorities to consider the issue of the availability and evaluation of new anticancer agents developed by industry: What drugs can be studied? When should their evaluation in children begin? How should they be developed?

Current trends in the regulatory context promote this procedure. The European Agency for the Evaluation of Medicinal Products (EMEA) has developed and distributed for comments an "Addendum on pediatric oncology" to its "Note for guidance on the evaluation of anticancer medicinal products in man".[2] This text describes new recommendations for the development and thus the registration of anticancer agents. The final version of the paediatric addendum should be adopted by the end of 2003. A European regulation on paediatric medicinal products is currently being drafted. This law, like the regulatory initiatives in effect in the US since 1997,[3] is intended to promote the evaluation of drugs in children, by proposing, in particular, incentives for the companies that develop them. In the domain of oncology, this regulation should thus improve access to innovative treatment for children with malignant tumours and a poor prognosis.

The European Union has identified the assessment of new anticancer agents for children as a major public health goal. This objective can be attained only if a partnership is developed between paediatric oncologists, parents, pharmaceutical companies and regulatory authorities.

We thus began by taking an inventory of clinical research in paediatric oncology and haematology. On the basis of our analysis of four types of drugs and their development processes, we drafted recommendations for the development of new anticancer agents for children (excluding cell therapy).

The studies still needed for the chemotherapy drugs currently in use in paediatric oncology[4] were not considered: The Committee for Pediatric Orientation of the French agency for the sanitary safety of health products (Afssaps [Agence française de sécurité sanitaire des produits de santé]) is now examining them. Similarly, studies of treatment strategies and non-interventional trials (as defined by European Directive 2001/20/EC[5]) were not discussed, although these topics cover a substantial portion of the clinical research in paediatric oncology. They require their own independent analysis, consensus and recommendations.

2. Inventory

2.1 The Disease

Childhood and adolescent cancers are rare diseases. They account for 1% of cancers, that is, 1800 new cases per year in France and 12 000 in Europe. More than 60 different diseases have been identified, but ten of them account for 90% of the cancers observed in children and adolescents: 40% are leukaemias and lymphomas and 60% solid tumours (table I).

While some of these diseases are specific pathological entities (leukaemia, lymphoma, some brain tumours, sarcomas, malignant germ cell tumours) common to children and adults,[7] others are specific to children (e.g. neuroblastoma, nephroblastoma, hepatoblastoma). Paediatric tumours are most often undifferentiated or only slightly differentiated, with a high potential for proliferation; this explains in part why they appear more sensitive to chemotherapy than cancers in adults. Similarly, specific genetic anomalies exist for some paediatric tumours,[8] such as the amplification of the N-myc oncogene in neuroblastoma or the EWS-FLI translocation in Ewing tumours. Each genetic marker constitutes a potential treatment target for new anticancer agents.

These diseases are very sensitive to chemotherapy. The overall cure rate is approximately 70% for all childhood cancers considered together. There are, nevertheless, substantial differences: from a median survival of 9 months for children with brainstem tumour[9] to a cure rate exceeding 95% for nephroblastoma (kidney tumour).[10]

Table I. Distribution of cancers before the age of 15 years (National Cancer Institute's Surveillance, Epidemiology, and End Results [SEER][6])

Disease	% of all cancers
Leukaemia	31.50
Brain tumours	20.20
Malignant Hodgkin's and non-Hodgkin's lymphoma	10.70
Neuroblastoma and other tumours of the sympathetic nervous system	7.80
Soft-tissue sarcoma	7.00
Nephroblastoma and other renal tumours	6.30
Bone sarcoma	4.50
Malignant germ-line tumours	3.50
Renal carcinoma	3.50
Retinoblastoma	3.10
Hepatoblastoma	1.30
Other	0.50

We must note that although the cancer cure rate is about 70%, the treatment (surgery, chemotherapy, radiation therapy) can cause life-long sequelae. This is an important social issue. It is estimated that in 2010, 250 000 adult Europeans aged 19–50 years will have been cured of a childhood cancer; it is therefore essential to improve the quality of these cures.

Cancer remains the leading cause of death by disease in children older than 1 year. Each year, more than 3000 children in Europe die of cancer. Among the tumours with a poor prognosis are the high-risk leukaemias, most brain tumours, and the metastatic and high-risk forms of the most frequent paediatric tumours (neuroblastoma and bone and soft-tissue sarcomas).

Accordingly, the objectives of paediatric oncology are clear:

- increase the cure rates for the poor-prognosis malignancies;
- improve quality of life during treatment and the quality of recovery for the diseases with a good prognosis.

2.2 Clinical Research

Structures for clinical research in paediatric oncology and haematology have been developed over the past 40 years. Networks now exist at the national, European and international levels. The International Society for Pediatric Oncology (Société Internationale d'Oncologie Pédiatrie [SIOP]) has conducted several treatment trials on malignant mesenchymal tumours[11] and on nephroblastoma.[10] A phase III trial for Burkitt lymphoma has just been completed in France, Great Britain and the US. In France, three separate groups and societies had focused on solid tumours (the French Society of Pediatric Oncology [Société Française d'Oncologie Pédiatrique or SFOP]) and on leukaemia (the FRALLE [French Acute Lymphoblastic Leukaemia Group] and EORTC [European Organization for Research and Treatment of Cancer] groups), but they merged in December 2002 into a single society, the French Society for Childhood and Adolescent Cancer (Société Française des Cancers de l'Enfant et de l'Adolescent [SFCE]), to combine their efforts and provide a better approach to the issues involved in management of child patients, clinical research and ethics.

The low incidence of these diseases explains the need to work in networks that can provide synergy between centres to optimise the response to each child's particular situation and can conduct prospective assessments of new treatments in the best possible conditions. This leads to a very high rate of participation in research: 70% of young patients are included in a clinical research programme, but fewer than 10% of adult patients. The clinical research in paediatric oncology principally involves evaluation of treatment strategies rather than development of new drugs. The most common types of studies are non-interventional (defined in European Directive 2001/20/EC[5]). Randomised phase III trials are relatively unusual, because of the rarity of the various diseases (they would require large multicentre trials for long periods, often exceeding 5 years) and the existence of treatment strategies that are efficacious, tested and acceptable in terms of sequelae. Because they are directed only at patients who have already experienced treatment failure, phase I and II studies of new drugs or new combinations concern a relatively small portion of patients. Finally, 'practice surveys' or 'cohort surveys', assessing the long-term sequelae of treatments, are set up regularly.

Table II. Number of trials reported to the French agency for the sanitary safety of health products (Afssaps [Agence française de sécurité sanitaire des produits de santé]), 1998–2002

All types of trials	≈1500/year
Haematology/oncology, adult	≈200/year
Paediatrics	≈110/year
Haematology/oncology, paediatric	≈12/year

Philippe Vella presented an inventory of the clinical research activity reported to Afssaps for 1998–2002 (table II). Each year, on average, 12 trials in the area of paediatric haematology/oncology were reported to Afssaps and 110 trials involving children with any disease. During this period, pharmaceutical companies sponsored 80% of the trials, including those in paediatrics. The situation is very different in oncology, however, as industry sponsors only 55% of the trials for adults and a mere 16% of those for children (figure 1).

This furnishes proof of one of the points discussed below: the low level of investment by the pharmaceutical industry in paediatric oncology research and the paucity of approved drugs in this domain. The paediatric information available in the summary of product characteristics is limited, if not poor, for many of the chemotherapy agents used daily for the treatment of childhood cancers.[4]

2.3 Early Treatment Research

Research groups in France and in Europe have devoted much effort over the past 10 years to developing new anticancer agents for patients who have relapsed or have been refractory to all treatment. Accordingly, since 1995, the SFOP Pharmacology Group has conducted work in new drug development, often in collaboration with the New Agents Group of the United Kingdom Children's Cancer Study Group (UKCCSG), with industrial partners. In 7 years, ten drugs have been evaluated in 17 trials – phase I, phase II or pharmacokinetics. This represents 559 study participations, 64% in France and 36% in Great Britain. Among these ten drugs, eight had never been used in children before and four had no marketing approval at the time the paediatric study began.

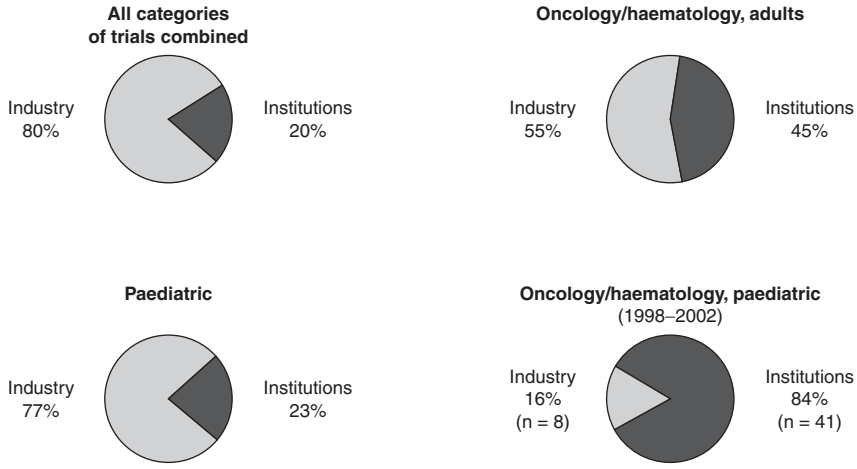

Fig. 1. Sponsorship of trials reported to the French agency for the sanitary safety of health products (Afssaps [Agence française de sécurité sanitaire des produits de santé]) 1998–2002.

The duration of phase I or II studies ranged from 9–44 (median 28) months for 12–81 (median 28) patients per study. Of the molecules studied, irinotecan (Campto®)[12,13] and temozolomide (Temodal®)[14] have undergone fairly complete development, including preclinical studies modelled on those of xenograft for paediatric tumours, and phase I and phase II trials of these agents, either alone or in combination. In addition, very regular exchanges take place with the US and have already led to the establishment of an international consensus on the conduct of phase I trials in children.[15]

2.4 Industry and Clinical Research in Paediatric Oncology

Paediatric anticancer agents are developed only rarely. Paediatric data were included in the applications for only 2 of the 26 agents that have obtained centralised European approval since 1995 for an indication related to cancer. These were temozolomide for the treatment of recurrent malignant glial tumours and rasburicase (Fasturtec®) for the treatment of tumour-induced hyperuricaemia.[16] Two essential factors may explain the paucity of drugs developed by the pharmaceutical industry for registration for indications in paediatric oncology.

First, because of the incidence of cancer in adults in France (270 000 new cases per year) compared with that in children (1800 new cases per year) and because the cure rate is still below 50% in adults, new drugs are first assessed in the most prevalent adult diseases, none of them common in children: cancers of the breast, lungs, colon and prostate. The cost of clinical development – from the preclinical stage to registration – is such ($US500 million up to the first authorisation) that the return on investment is evidently always assessed, and the balance is only rarely positive for paediatric indications. The risk of a long recruitment period for trials, a market considered small, the complexity of introducing new drugs into the treatment arsenal in paediatrics, and a field that is multidisciplinary and already very intensive add to these economic considerations.

This should change in the decades to come, with the development of targeted molecular and genomic approaches enabling the selection of groups of patients really able to benefit from a given treatment. This 'niche' approach should therefore be developed and should help in improving the return on investment.

We should also stress that risk-taking is important for drug companies. As mentioned above, approximately 60 distinct pathological entities have been identified in children; ten of these tumour types account for more than 90% of cases and the others occur at a low incidence. Clinical screening for diseases potentially sensitive to a given agent is therefore necessarily complex and long. Finally, a presumption of acute or long-term toxic risks in children may be thought to harm the image of the product.

The second factor is methodological. The standard development methods used for common indications in adults are not easily adapted to diseases occurring at a low incidence and for which the benefit-to-risk ratio is assessed still more strictly. Even the most modern methodology (such as the Continual Reassessment Method)[17] has not yet really entered current practice. The pharmacological evaluation of drugs by age group can also impede these assessments and thus make the protocol and the interpretation of results more complex.

2.5 The Regulatory Environment in Europe

Trends in the regulatory environment in Europe, similar to what has already taken place successfully in the US, should en-

able larger and better evaluation of the possible treatment options for children with cancer.

Regulations for orphan drugs for the treatment of rare diseases went into effect in Europe in 2000. From August 2000 to October 2002, 43 of 118 orphan designations (36%) concerned a malignant disease or a condition related to cancer.[18] Cancer is the leading medical domain in terms of approval of 'orphan' designations by the EMEA Committee of Orphan Medical Products (COMP). On the other hand, only two have concerned a disease specific to children, while 16 involved diseases observed in both children and adults.

The paediatric addendum of the "Note for guidance on evaluation of anticancer medicinal products in man"[2] has been released for comment, and the final version is expected to be adopted by the end of 2003. These recommendations underline the role of preclinical evaluation in paediatric drug development[19] and specify the particularities of clinical evaluation in children, particularly in terms of the methodology for phase I trials.

The European Commission is currently drafting a European regulation on paediatric drugs. The European Union Council of Ministers approved a resolution on December 14, 2000, that invited the Commission to make proposals "in the form of incentives, regulatory measures or other supporting measures to ensure that medicinal products for children are adapted to the specific needs of that population group, taking account of the ethical aspects of clinical trials".

In the US, measures went into effect in 1997 to encourage pharmaceutical companies to study drugs in children.[3] The US FDA addresses to the pharmaceutical company a written request concerning a drug for which it wants information about its effect in children. If the company provides study results to the US FDA, its exclusivity for the active compound, in all indications, forms and doses, is extended for 6 months. This so-called paediatric exclusivity is obtained regardless of whether the results of the paediatric study are positive or negative. The availability of appropriate information for paediatric use is clearly the objective of this regulatory incentive procedure, which has proved very effective. By May 2002, more than 250 written requests had been made, 25 in oncology, and 57 extensions of paediatric exclusivity were attributed, including one in oncology.

The European initiative is inspired by this North American experience. The European directive on paediatric drugs is expected for 2005. It will, it is hoped, significantly increase the evaluation of drugs for children in Europe, particularly of new drugs to treat serious, potentially fatal diseases, such as cancer.

3. Examples of Development

3.1 Two Situations Distinguished

Distinction is made between supportive care treatments (e.g. analgesics, antiemetics, growth factors) and anticancer drugs. Indications for the former are identical in adults and children. While they may have some specificities in their development for children (forms, dose-finding, age groups, outcome measures), these are not specific to haematology/oncology, but to paediatrics in general. This topic was the subject of a round table at Giens in 2002.[20]

Anticancer drugs constitute a specific category within the framework of paediatric drugs. The development strategy for an agent differs according to whether its target is a disease, even rare, present in children and adults (e.g. chronic myeloid leukaemia [CML]) or whether the same agent targets different diseases in adults and children.

Four types of agents were identified among the technological advances currently under evaluation:

- the classic cytotoxic agents, with a narrow benefit-to-risk ratio, developed at the maximum tolerated dose (e.g. irinotecan);
- agents effective at an optimal biological dose (e.g. gefitinib [Iressa®]);
- targeted agents, for which the presence of the target conditions the treatment activity (e.g. imatinib mesylate [Glivec®], rituximab [Mabthera®]);
- and, in this latter group, agents whose target is a specific molecular abnormality of a paediatric tumour (such as the EWS-FLI translocation for Ewing tumours).

It is estimated that more than 90% of the drugs that will require evaluation in children in the next 10 years will belong to one of the first three categories and will be developed first in adults, while at most 10% of the agents developed in children will have a specific paediatric target. A prerequisite for development of the latter category is a major effort to better understand the biology of paediatric tumours, through the use of genomics and proteomics, and to identify molecular anomalies as potential treatment targets. Such programmes will most likely be conducted, initially, by academic researchers, before partnerships are created with pharmaceutical companies to pursue 'drug screening and discovery' programmes.

3.2 Irinotecan (Campto®)

A standard cytotoxic agent that inhibits topoisomerase I, irinotecan was first approved in 1995 and then in 1998 for adults with metastatic colorectal cancer. Its development in gastrointes-

tinal diseases continues. A preclinical evaluation for paediatric tumours took place in an academic-industrial partnership.[12]

Aventis sponsored a phase I clinical trial for solid tumours in children in 1997, and then a phase II trial for children with rhabdomyosarcomas, neuroblastomas and medulloblastomas. The data collected in these trials will be submitted to the European Health Authorities to be integrated into the summary of product characteristics (internal data furnished by the moderator).

3.3 Imatinib Mesylate (Glivec®)

This 'targeted molecule' inhibits tyrosine kinase (TK) Bcr-Abl, a protein essential to the development of CML. Imatinib mesylate also inhibited the TK of the cKit receptor, which mediates the growth of gastrointestinal stromal tumour cells. The specific diseases for which imatinib mesylate is authorised are Philadelphia-positive CML and malignant gastrointestinal stromal tumours that are metastatic and/or inoperable and positive for Kit(cd117).

The registration file (2002) includes data on tolerability, efficacy and pharmacokinetics in 34 children with CML or leukaemia and included in the phase I trials. Phase II trials of CML in children are under way.

3.4 Gefitinib (Iressa®)

Gefitinib is the leading product in a new category of treatment – an inhibitor of TK activity in the epidermal growth factor receptor (EGFR). It selectively inhibits, via EGFR, a cascade of reactions essential in the transmission of the signals for tumour proliferation, growth and survival. Administered orally, gefitinib has so far been developed for the treatment of advanced stage non-small-cell lung cancer and is approved in Japan for this indication in adults. The drug is also being developed for several other solid tumours that express EGFR. A phase I paediatric study is under way in the US.

3.5 Rituximab (Mabthera®)

This targeted molecule is a chimeric murine/human monoclonal antibody aimed at the CD20 antigen, a protein located on the surface of malignant B lymphocytes. It interrupts the pathological proliferation of these cells. It is currently indicated for diffuse large B cell CD20+ lymphoma, combined with CHOP (a standard chemotherapy: cyclophosphamide, adriamycin, oncovin and prednisolone). Paediatric trials are under way.

4. Recommendations

Children and adolescents should benefit from the new treatments that will be developed in oncology over the next 15 years. Numerous new anticancer agents, with innovative mechanisms of action, are already under study in adults.

To reach this important public health objective, it is necessary to:

- increase the number of anticancer agents assessed while guaranteeing the protection of children and adolescents and meeting all ethical standards;
- reduce the delay in access to these new agents;
- shorten the duration of trials.

4.1 When Should Paediatric Development Begin?

This is a difficult but crucial question, as all the round table participants stressed. Many factors are relevant in deciding the optimal point for beginning paediatric studies. The participants considered it necessary, however, to change the situation observed in recent years for the development of new anticancer agents in children: never or too late, that is, after the initial approval.

Paediatric tumours often respond differently from tumours in adults to the same chemotherapy drug. It is for this reason that initiation of paediatric development of an anticancer agent must not depend on its efficacy in adult disease.

The round table therefore recommends that the paediatric development of anticancer agents begins *before* the first application for marketing authorisation.

Adequate safety and tolerability data must be available and collated for adults, before development can begin in children. This should be after the phase I trials, and optimally during phase II trials. The benefit-to-risk analysis, in compliance with the European Directive on Good Clinical Practices (Directive 2001/20/EC[5]), is an important element of this implementation.

The round table recommends that biological (research and validation of treatment targets) and/or efficacy (preclinical pharmacology) studies be conducted before paediatric studies begin, on relevant models of paediatric tumours, in order to:

- help choose the molecules for which development in children is justified, on preclinical bases;
- bring together, if appropriate, the elements required for a waiver (in the framework of the European paediatric drug regulations) on condition that the studies conducted are adequate in terms of quality, quantity and relevance of information.

The round table recommends that preclinical evaluation for children be considered for every agent or category of agents that

begins development for adults. This recommendation is consistent with the paediatric addendum to the EMEA "Note for guidance".[2] This would make preclinical data available and a rational basis for decision possible at the point that the molecule continues its development for adults and when the question of paediatric development is raised.

The additional toxicological studies specific for children, particularly for agents administered over a long period, should be discussed and performed when necessary.

In this strategy, when development in adults is successful, the first marketing authorisation application can be filed with paediatric data. If development in adults fails and is abandoned, the agent can be registered as an orphan drug if it is active against one or more paediatric tumours.

4.2 How Can Paediatric Development Be Improved?

1. Create a coordinated and integrated laboratory network to conduct preclinical biological and pharmacological evaluations of new anticancer agents. This network should use a panel of paediatric tumours and validated models as well as the most advanced technologies to characterise the targets, the mechanisms of action and the treatment activity, and thus define priorities in terms of choices of molecules or indications or both.

The round table recognises the known and potential limits to the predictivity of these studies and these models. A prospective evaluation of their pertinence is necessary.

2. Set up a plan for paediatric development. This plan must consider the paediatric dimension from preclinical evaluation and dose-finding onward to its possible use in this or that disease; it must position the agent as improving the prognosis of serious diseases, or substituting for toxic agents in diseases that currently have a good prognosis but a high risk of long-term sequelae. It must be discussed and developed early during development for adults, for example, when the decision to begin human studies is made. A partnership between paediatric oncologists, industry and regulatory authorities must be created for this purpose.

The round table stresses the need for cooperation between these partners early during the clinical development of anticancer agents.

3. Improve recruitment to reduce the duration of phase I–II trials. For this, the round table recommends:

- Creation of a European network of early clinical research to increase the number of study centres, particularly for phase II trials, which, while complying with Good Clinical Practices (European Directive) and the International Conference on Harmonisation (ICH) recommendations, are not as restrained by methodological requirements.
- Improvement of the information available about ongoing trials, particularly through internet sites such as those of Orphanet[21] or Afssaps[22] but also information for parents and children about clinical research (round table no. 1, Giens 2002[23]); participation by parents and parent associations must also increase.
- Better use of adult data, particularly in terms of pharmacokinetic and pharmacodynamic relationship, to optimise dose-finding in children. Data from adults are not currently extrapolated to children in studies of cytotoxic chemotherapy. This must be implemented for the new anticancer agents used at their optimal biological dose and not at the maximum tolerated dose. This would make it possible to reduce the number of subjects needed to define the recommended dose for children.
- Develop methods useful for reducing the number of necessary subjects. This is a requirement common to rare diseases and is most difficult for the rarest diseases.

Genotyping patients in early studies is important to help elucidate the optimal conditions for subsequent use of the agent.[24] It is not specific to children, but must be systematically considered.

The objective is to make paediatric data available at the moment the marketing authorisation dossier is filed. In the US, as pointed out above, incentives apply whether or not the agent is efficacious in children.

4.3 How Should a Drug Be Registered for a Specific Malignant Childhood Disease?

The conditions for registration for specific childhood diseases could not be discussed in detail during the round table, because time ran out. The following particularities must be considered:

- the existence of non-exhaustive data for children when the application is filed;
- the practical and ethical impossibility of conducting in children a randomised phase III study to compare an anticancer agent alone with the best current treatment;
- the possibility and conditions for supplementary postmarketing authorisation studies;
- the issue of evaluating long-term tolerability.[20]

5. Conclusion

Assessment of the new anticancer agents in children and adolescents is a public health issue, identified as such by the European Union. Only cooperation and work in partnership between academics, parent associations, pharmaceutical companies and

regulatory authorities will enable these objectives to be attained. The round table, by the richness of the discussions, the sharing of experience, and the production of consensus recommendations, demonstrated the feasibility of these partnerships as well as the willingness and investment of all the participants.

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