THE IMPORTANCE OF CLINICAL TRIALS IN THE FIGHT AGAINST HISTIOCYTOSIS

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History and description of clinical trials, as well as an outline of obstacles to successful clinical research

Introduction

Over the last 30 years, the survival for children affected by cancer has dramatically improved. A number of factors have contributed to this remarkable success story, including the availability of new, more effective chemotherapy drugs and treatment regimens, the emergence of promising new techniques such as bone marrow transplantation, and improvements in supportive care measures, including better antibiotics and better transfusion support. However, the single biggest reason for success in the battle against childhood cancer has been the long-standing and widespread participation of childhood cancer patients in clinical trials. National and international clinical trials for children with cancer have been sponsored by the International Society of Pediatric Oncology (SIOP), the National Wilms Tumor Study Group (NWTS), the Children's Cancer Group (CCG), the Pediatric Oncology Group (POG), and other national and international groups focused on childhood cancer. The 4 large childhood cancer groups based in the United States have recently merged into 1 clinical trials group focused on childhood cancer, the Children's Oncology Group (COG).Currently, over 90% of children in North America less than 15 years of age receive their care at institutions affiliated with COG; the majority of these patients are enrolled in clinical trials.

Children with Langerhans cell histiocytosis (LCH) or hemophagocytic lymphohistiocytosis (HLH) have not, until recently, had the same opportunities to benefit from participation in clinical trials as have children with cancer.

What is a Clinical Trial?

A clinical trial is a treatment protocol which combines state-of-the-art treatment with clinical, or patient-oriented, research. Clinical trials are the means by which new treatments are evaluated to determine if they are better than currently available treatments. Studies have demonstrated that childhood cancer patients participating in clinical trials have, in general, better outcomes than patients who do not participate in such studies.13 Clinical trials are distinguished from treatment protocols by the elements of 1) peer review for human subjects' protection and scientific merit by an institutional review board (IRB) and, often, a separate scientific review board; 2) informed consent by participants and their guardians; 3) strict adherence to a defined protocol of eligibility, evaluation, and treatment; and 4) prospective, accurate, and complete collection and reporting of data. For more information regarding clinical trials, please visit the National Cancer Institute's Clinical Trials website.

The Era Before the Histiocyte Society

<u>Langerhans Cell Histiocytosis</u>

LCH has been exposed to a wide range of therapeutic strategies over time, reflecting the changing understanding of the disease process.8, 10 During the 1960s, LCH was thought to be a malignancy, and this opened the era of cytotoxic therapy for this disease. A number of single- and multi-agent therapeutic regimens consisting of steroids and cytotoxic drugs were applied with varying success. Unfortunately, most of the published papers reflected retrospective single-institution experience with a limited number of observations collected over long periods of time. Significant contribution to a better description of disease manifestations, collection of knowledge about the variable natural history, elaboration of treatment

schedules, and improvement of the overall prognosis brought multi-institutional studies conducted between the 1950s and 1970s.

However, due to lack of uniform criteria for patient evaluation and stratification, the patient population reports varied greatly with respect to extent of disease. This precludes precise comparison of the reported data and makes any conclusions regarding superior treatment approaches at best, tenuous. Nevertheless, clinical studies from this time period brought some very important observations, which formed a basis for development of new therapeutic strategies and design of large-scale prospective trials.

The largest cooperative prospective clinical trials of the 1980s were those of the Italian AIEOP Group (AIEOP-CNR-HX 83)2 and of the DAL-HX group (DAL-HX 83)5, both applying systemic chemotherapy promptly after establishing the diagnosis of LCH. Overall mortality was low in both these series (8% and 9%, respectively). The low incidence of disease reactivation seen in the DAL-HX 83 trial (overall 23%) provides evidence that intensive treatment started early may beneficially influence the natural course of the disease. Disease related permanent consequences were encountered in 48% of patients in the AIEOP series and in 33% of the DAL group. Strikingly, diabetes insipidus (DI) occurred in only 20% and 10% of the cases, respectively.

It appeared that a breakthrough in the management of LCH could be easily achieved. However, in the 1980s, LCH has been accepted to be a reactive rather than malignant disease, and there has been loss of interest in it. As a result, funding and conduction of clinical trials became difficult, and LCH fell into the category of “orphan diseases.”

Hemophagocytic Lymphohistiocytosis

The term HLH includes 2 different conditions, namely, the primary or familial HLH (autosomal recessive disorder) and secondary HLH (infection-or malignancy-associated). Primary HLH is most commonly seen in infancy and childhood. In both forms of HLH, there is an exaggerated and persistent interplay of immune cells leading to hypercytokinemia and organ damage. Without treatment, primary HLH is a rapidly progressive disease with ultimately fatal outcome within week to months. This is true also for most cases of secondary HLH. Initial therapeutic attempts using cytotoxic agents met with only moderate success. Plasma or blood exchange brought about transient responses. Chemotherapy with epipodophyllotoxins and immunosuppression directed at the activated T-lymphocytes have proved to be effective in achieving remissions of HLH. However, the majority of the patients experience relapse, and the only curative option available to date is the allogeneic stem cell transplantation. Before the development of effective treatment, the survival rate for patients with HLH was less than 10%.

The Era of Active International Cooperation

Clinicians and basic scientists with great interest in the histiocyte and its disorders met in 1985 at an historic international workshop in Philadelphia, which led to foundation of the Histiocyte Society. This international Society has provided a forum for the exchange of information and a framework for organized activities of fundamental importance.

As a result of the collaborative efforts, some “white papers” have been published by the Histiocyte Society 3, 17, 18. Additionally, a simple stratification system for practical use has been introduced for LCH. Diagnostic guidelines for HLH were elaborated, which enable timely diagnosis and early therapy for this rapidly fatal condition. Through these early activities, a common language, uniform classification, standardized diagnostic criteria, and guidelines for patient evaluation and followup have been settled and have achieved worldwide popularity and acceptance. Aside from the self-evident benefits of accurate communication between physicians and comparison of results obtained by different treatment centers, the main purpose of the Histiocyte Society was to facilitate large-scale cooperative international studies.

The Histiocyte Society, recognizing the importance of clinical trials in identifying more effective treatments for children and adults with LCH, HLH, and other forms of histiocytosis, has organized and is conducting international clinical trials for children and adults with histiocytosis. These clinical trials provide the only

possible means of addressing a number of critical questions about the best methods to treat LCH and other forms of histiocytosis through evidence-based research. These trials also offer an opportunity to improve researchers' understanding of the underlying causes and biological features of the histiocytoses through the collection of specimens for research studies. Increased registration of children and adults with histiocytosis in well-designed clinical trials will lead to more rigorous and rapid evaluation of promising new treatments.

LCH-I Trial

In 1991, the Histiocyte Society opened its first clinical trial for the treatment of Langerhans cells histiocytosis, LCH-1. This clinical trial was truly an international effort, enrolling over 500 patients (148 of them were eligible for randomization and treated with the trial regimen) from Europe, South America, and North America. LCH-I compared the effectiveness of vinblastine (Velban) with etoposide (VP-16) in the treatment of patients with multisystem LCH. The basis for planning and initiating this study was the observation by a number of histiocytosis experts that etoposide was an effective treatment for some patients with recurrent LCH who had failed other treatments such as vinblastine. This suggested that etoposide might also be more effective therapy than vinblastine in patients with newly diagnosed LCH. The LCH-I clinical trial was designed to answer this question. The results of LCH-I have been published.4 The study concluded that vinblastine and etoposide are equivalent treatments for children with newly diagnosed LCH. However, because of more recent observations which have linked etoposide with an increased risk for the development of secondary leukemia, vinblastine has remained the preferred treatment by most physicians.

An unexpected and important new finding made during the conduct of this study illustrates the importance of clinical trials participation: LCH-1 demonstrated that children with high-risk disease who do not respond to the initial 6-week treatment are at significantly increased risk of ultimate treatment failure. Identification of this new prognostic factor may lead to the development of improved treatments for higher-risk patients, while sparing lower-risk patients unnecessary toxicity. Although LCH-I was successfully completed, few physicians or patients in North America participated in the study.

LCH-S Trial

The Histiocyte Society also organized and opened LCH-S, a clinical trial for children with refractory or progressive LCH. This study was opened concomitantly with LCH-I and sought to address 2 important clinical questions: (1) to determine whether a role exists for bone marrow transplantation in children with refractory or progressive LCH who have a matched sibling donor and (2) to confirm anecdotal reports of the success of cyclosporine A in children with refractory or progressive LCH who lack suitable donors for marrow transplantation. Unfortunately, the LCH-S clinical trial had to be prematurely closed due to insufficient patient enrollment. Thirteen patients had been treated in the immunosuppressive arm of the trial (antithymocyte globulin, prednisone and cyclosporine A). 12 Nine of these patients (69.2%) died at a median of 3 weeks. It is possible that potential efficacy of this regimen had been hampered through late-therapy switch (median time after diagnosis 5 months), and hence heavy pre-treatment and disease-related tissue damage. The small number of patients precludes a precise assessment of the regimen, and the limited experience is quite disappointing.

LCH-II Trial

Following the successful completion of LCH-I, a followup study was developed which built upon the results of LCH-I. LCH-II was a randomized phase-III trial for patients with multisystem LCH considered to be at higher risk of disease progression or recurrence. LCHII sought to more clearly define the additive role of etoposide in the treatment of high-risk LCH, using a different approach than was taken in LCH-I. The LCH-II clinical trial compared, in a randomized fashion, the effectiveness of the combination of vinblastine, oral prednisone, and mercaptopurine, to the same combination with the addition of etoposide. Also in LCH-II, patients were stratified into lower or higher risk groups based on their extent of disease at the time of diagnosis. Almost 900 patients were registered onto LCH-II. The results of LCH-II are expected to soon be published.

LCH-S-98

The LCH-S-98 study was a nonrandomized single-arm protocol which sought to confirm the activity of 2-chloro-2'-deoxyadenosine (2CdA) in patients with recurrent or progressive LCH following standard therapy. Based upon anecdotal reports in the medical literature, the use of 2CdA for recurrent or progressive LCH appears to hold great promise. 16 However, these exciting preliminary findings, together with information regarding the optimal dose and schedule for the administration of 2CdA and its acute and long-term toxicities, need to be confirmed in a prospective clinical trial with patients who are treated and evaluated in a uniform fashion. The LCH-S-98 protocol has been recently closed to patient accrual. The final data have not yet been published, but preliminary data evaluation showed that monotherapy with 2CdA does not significantly improve prognosis in patients with severe progressive LCH. New clinical trials for patients with progressive or recurrent Langerhans cell histiocytosis are currently being developed by the Histiocyte Society.

HLH-94 Trial

The HLH-94 study represented the first comprehensive, prospective treatment trial for patients with HLH. This study opened in July 1994 and enrolled over 300 patients (113 eligible trial patients) from 27 countries prior to its close in 1998. This study combined chemotherapy and immunotherapy (etoposide, corticosteroids, cyclosporine A, and, in selected patients, intrathecal methotrexate), followed by bone marrow transplantation (BMT) in persistent, recurring, and/or familial disease. 6 The overall survival in this study was 56% after a median observation time of 37.5 months. The immunochemotherapy (initial and continuation) was successful in 88/113 (78%), in that they were either admitted for BMT (n=65) or were still alive at last followup (n=23). Forty of the 65 patients (62%) who underwent bone marrow transplantation survived. These results show that HLH-94 treatment is very effective and has achieved its primary goal, namely to improve survival of HLH. Thanks to the combined approach of HLH-94, it is estimated that 60% of the patients will survive their disease. This achievement underscores the importance of international collaboration in conducting clinical studies on rare disorders.

LCH-III

The LCH-III protocol was a randomized phase-III trial for patients with multisystem LCH considered to be at high risk of disease progression or recurrence. The LCH-III study began enrolling patients in 2001. LCH-III was built upon the success of its predecessor studies by evaluating the relative efficacies of 2 multi-agent treatment regimens for high-risk LCH. The clinical trial sought to determine whether methotrexate improved the outcome of patients with high-risk LCH, and to define optimal treatment for patients with lower-risk disease, such as multi-focal bone disease.

LCH-S-2005

About 20% of the patients with multisystem LCH did not respond to the available first-line treatment and had extremely poor prognosis. A Phase II prospective trial LCH-S-2005 for patients with severe disease (involvement of liver and spleen, as well as hematopoiesis) who did not respond to at least 6 weeks of “conventional” therapy, was taken into process. The study was expected to be based on a promising preliminary experience with the combination of 2-CdA (cladribine) and cytosine arabinoside1 with the main objective to assess the efficacy of this combination in LCH patients with extremely poor prognosis. As the combination was expected to be very toxic, strict eligibility criteria was defined.

LCH Adult-I

The LCH-A-I clinical trial opened on October 1, 2004. Goals included: 1) defining a uniform initial evaluation for adults with single-system disease, CNS lesions, isolated pulmonary disease, and multisystem LCH; 2) evaluating the effectiveness of a standard multiagent chemotherapy protocol in adults with multisystem LCH; and 3) evaluating the effectiveness of smoking cessation and of steroid therapy in adults with isolated pulmonary LCH.

Current Clinical Trial Conducted by the Histiocyte Society

A clinical trial developed by the Histiocyte Society for patients with HLH is currently open.

HLH-2004

The HLH-2004 study represents the second comprehensive, prospective treatment trial for patients with HLH. This international study, which opened to patient enrollment in January of 2004, is a further refinement of the highly effective therapy which was evaluated in HLH-94, 6 with the goal of further increasing the long-term survival rate in this disease.

Obstacles to the Success of Clinical Research for Histiocytosis

Given the availability of well-designed clinical trials for children with LCH and HLH and the recognized importance of clinical trials in identifying more effective therapies for these patients, what are the obstacles which threaten their successful completion?

1. A lack of awareness, on the part of both patients and their physicians, of the availability of clinical trials for histiocytosis.

   The Histiocyte Society is a small organization of physicians and scientists committed to improving the lives of patients with histiocytosis by conducting clinical and laboratory research into the causes and treatment of these disorders. Results from ongoing and completed studies for histiocytosis, as well as proposals for new clinical trials, are presented and discussed during the annual scientific meetings of the Society. However, attendance at these meetings primarily consists of a relatively small group of physicians and scientists who focus much of their time and effort on research related to histiocytosis. A much larger number of pediatric hematologists/oncologists who routinely treat children with histiocytosis are unable to attend Histiocyte Society meetings and thus may not be aware of the current status of the Society's clinical trials which are available to their patients.

   Measures taken to address this lack of physician awareness include the following: 1) mailings targeted for pediatric hematologists/oncologists and other physicians who routinely see patients with histiocytosis, announcing the opening of new clinical trials sponsored by the Histiocyte Society; 2) participation in annual professional Society meetings through exhibits; and 3) the development of this website which provides access to summaries of available clinical trials and contact information for patients and treating physicians who wish to obtain more information. However, the Histiocyte Society continues to rely heavily on the "word-of-mouth" approach among the hematology/oncology community to disseminate the availability of these trials.

2. A lack of understanding, or even fear, on the part of patients' families about participating in medical "research" trials.

   Many patients and their families are unfamiliar with the concept of clinical trials and may regard participation in any form of research as inappropriate medical experimentation. Parents sometimes state that they do not want their child to be a "guinea pig." Families may also harbor reservations that participation in a clinical trial will mean that effective treatment for their child's condition will be withheld, or that their child will receive experimental medications or other non-standard treatments without their knowledge or permission.

   The process of review and approval of clinical protocols by local institutional review boards ensures that all clinical research conducted at an institution meets local standards of scientific validity and ethical integrity. (This means all possible safeguards of the patients are part of the study.) The process of obtaining informed consent likewise ensures that an individual patient and his/her family are provided a full understanding of the proposed research, any costs and inconveniences which may be incurred by their participation, the potential risks and benefits of

participation in the proposed research, and their rights as subjects of medical research. Thus, concerns such as those listed above which are expressed by the families of children with LCH or HLH who are eligible to participate in clinical trials should be adequately addressed during the process of providing informed consent by their physicians.

3. A lack of resources, on the part of physicians, to support participation in clinical trials for histiocytosis.

   Most physicians appreciate and understand the importance and significance of clinical research. However, active participation in clinical research requires significant commitment of a physician's time and energy, typically with no reward beyond the satisfaction of knowing that he or she is contributing to the greater good. Preparation, submission, and revision of a clinical trial proposal to the local institutional review board is a time-consuming task. The unavoidable need for prioritization of many available protocols may dictate that submission of a protocol to the IRB for the occasional patient with LCH or HLH is superceded by those for patients with more common diseases such as acute lymphoblastic leukemia or neuroblastoma.

   Likewise, accurate collection of required clinical data and completion of the numerous data forms mandated by the study require additional time of physicians, nurses, and data managers, many of whom are already faced with excessive workloads as a result of continuing health care reforms. Continued submission of data may be difficult to justify in the absence of a system of "credits" or other incentives to encourage physicians to actively enroll their patients onto clinical trials. Many physicians therefore elect not to submit Histiocyte Society treatment protocols to their local IRBs, but instead select one of the regimens being investigated in the study as a guideline for therapy, and treat patients "off study" who are eligible for clinical trial enrollment.

   The Histiocytosis Association (the Association) and Histiocytosis Association of Canada (HAC) have begun to address the issue of financial support for clinical research of histiocytosis through recent implementation of a clinical research-expense reimbursement mechanism. In order to help defray the research costs associated with the conduct of clinical trials sponsored by the Histiocyte Society, the Association and HAC now provide limited reimbursements to clinical investigators in the U.S. and Canada, based on patient enrollment onto Histiocyte Society-sponsored clinical trials, to support the costs of data management and other administrative requirements incurred by their patients' participation.

4. A lack of understanding, on the part of physicians, of the importance of their patients' participation in clinical trials for histiocytosis.

   The widespread practice of treating patients who are eligible for clinical trials "off-study" with the same research protocols, due to the inconveniences and time demands associated with patient participation in clinical trials, addresses the short-term needs of both the physician and patient by providing them with a well-formulated treatment guideline. However, this common practice is a major factor in the slow rate of progress in clinical research for histiocytosis. Only patients who are actually registered onto clinical trials after providing informed consent, and whose completed data forms are submitted to the study center, will play an active role in identifying more effective therapies for LCH, HLH, and other histiocytic disorders. Physicians who choose to use Histiocyte Society protocols as off-study treatment plans have a moral obligation to support the Society's efforts to improve the lives of children with histiocytosis by submitting these protocols to their local IRBs, by encouraging patients to take part in the processes of informed consent and clinical trial participation, and by submitting accurate data for enrolled patients in a timely fashion.

5. The rarity of Langerhans cell histiocytosis and other histiocytoses.

   It is ironic that a common justification given by physicians for not submitting protocols for the treatment of LCH and HLH to their local IRBs is the rarity of the disease. The uncommon nature

of these disorders is precisely the reason that well-designed clinical trials are so desperately needed to achieve progress in their treatment. No single institution has enough patients with histiocytosis to conduct a randomized clinical trial which will allow the rigorous evaluation of a promising new treatment. Progress in treating LCH, HLH, and other histiocytoses will require the coordinated efforts of dedicated physicians around the world.

6. Lack of federal funding to support clinical and basic science research of the histiocytoses.

   A final obstacle facing the successful conduct of clinical research for LCH, HLH, and other histiocytic disorders is the scarcity of funding. Virtually all of the research grants targeted at histiocytosis during the last 20 years have been sponsored by the Histiocytosis Association and the Histiocytosis Association of Canada through their fundraising activities. The rarity of LCH and HLH, together with the indolent course of LCH in many patients, contributes to their low prioritization for federal funding of clinical research when compared to other childhood diseases. Only through the continued grassroots advocacy efforts of the Histiocyte Society, patient and parent organizations such as the Association and HAC, and physicians and families involved with histiocytosis patients, can the present low scientific priority for research related to the histiocytoses be changed.

Summary

The availability of well-designed clinical trials offers patients with LCH and HLH an opportunity both to receive state-of-the-art treatment and to contribute to improved outcomes for all patients with these diseases. The Histiocyte Society strongly encourages its colleagues in the pediatric and adult hematology/oncology communities to support its research efforts in the fight against histiocytosis by (1) submitting the Histiocyte Society's clinical trials to their local institutional review boards; (2) enrolling eligible, consenting patients onto these clinical trials or referring their patients to specialists who participate in these trials; and (3) submitting accurate study data for enrolled patients to the study centers in a timely manner. The dedicated efforts of physicians around the world are needed to make the dream of a cure for all patients with histiocytosis a reality.

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