HISTIOCYTE SOCIETY

ANNUAL NEWSLETTER

2003 ISSUE

AN INTERNATIONAL COMMUNITY DEDICATED TO RESEARCH AND TREATMENT

HISTIOCYTE SOCIETY PRESIDENT'S REPORT

Maarten Egeler, M.D., Ph.D.

What an exciting annual meeting we had in Porto, Portugal. Why exciting? Well, the quality of the presentations is getting scientifically better and better. The insight in the exciting world of chemokies and their role in Langerhans cell histiocytosis presented by Dr. Annels was an example of what we have reached within the Histiocyte Society. Bit by bit we will unravel the intriguing world of normal and abnormal trafficking and activation of these specific dendritic cells. We need this fundamental basis to improve our understanding of the pathophysiology leading to better treatment and in the end a cure. The two educational presentations of members of our Society, by Drs. Nicole Grois and Bengt Fadeel were another example of the increasing knowledge of our members. The work provided over the years by our own "Queen of CNS-disease in LCH" is exciting and needed. She has been the light in many families suffering with children with this devastating form of LCH. The presentation on apoptosis, reflected in HLH is the example of bridging the fundamental knowledge of spontaneous cell death and HLH. The work provided by the Stockholm group has been and is exciting and is followed by many families with HLH.

Besides these presentations, I was happily surprised by the quality of submitted abstracts and presentations. Whether we hear about mutations in the perforin gene or micro-arrays of Langerhans cells, the bottom-line is, we are constantly learning. The Nezelof Award to Dr. Filipovich's team in Cincinnati was awarded by the founding President of the Society, Dr. Christian Nezelof himself. The hard work by the histiocytoses-group in Buenos Aires, headed by Dr. Braier has lead to this year's Nesbit Award.

Before this years Annual Meeting a symposium on histiocytoses was organized within the International Society of Pediatric Oncology (SIOP). This symposium, similar as the yearly symposium within the American Society of Pediatric Hematology and Oncology (ASPHO) make a tremendous difference. There we reach our colleagues who treat patients with histiocytoses. We have to be realistic that patients with histiocytoses are 1 – 3% of patients within either the world of the pediatric immunology of pediatric hemato-oncology. So we cannot

expect that all our colleagues know the state of the art of histiocytoses. So at those more general meetings, providing an update of our knowledge is wonderful. At the SIOP meeting at least 300 colleagues were attending and the symposium was well received.

Finally, we are getting step-by-step closer in developing standardized treatment-protocols for the adult patient suffering from LCH. Under the devoted guidance of Dr. Maurizio Arico, we are getting there. This has also resulted in the attendance of two pulmonologists. As pediatricians we cannot treat the adults with LCH, although a few of us do anyway. However, in the perfect world they are taken care of by medical hematologists and pulmonologists.

Representatives of 20 countries attended this years meeting, another example of the global problem of histiocytoses. Thirteen representatives of several Family Associations show the nice interaction between us, the physicians and researchers on the one side and the families on the other side. This first year as your President has been a learning experience. Some items went much better than expected; some were just very difficult indeed. However, for the coming two years you can still count on . . . ME

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Sir James Spence Institute—Newcastle upon Tyne, UK

Finn Wesenberg
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HISTIOCYTE SOCIETY STUDY GROUPS

HLH Study Group
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Karolinska Hospital—Stockholm, Sweden

Epidemiology Study Group
H. Stacy Nicholson, Chair
Oregon Health & Science University—Portland, Oregon USA

CNS Study Group
Nicole Grois, Chair
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LCH-S Study Group
Sheila Weitzman, Chair
The Hospital for Sick Children—Toronto, Ontario Canada

LCH III Study Group
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St. Anna Children's Hospital—Vienna, Austria

Adult Histiocytosis Study Group
Maurizio Arico, Chair
Ospedale dei Bambini—Palermo, Italy

Pathology Study Group
Ronald Jaffe, Chair
Children's Hospital—Pittsburgh, Pennsylvania USA

Malignant Histiocytosis Study Group
Peter Bucsky, Chair
Medical University of Lubeck—Lubeck, Germany

ANNOUNCEMENTS

XIX Annual Meeting of the Histiocyte Society

September 18–20, 2003

Philadelphia, Pennsylvania USA

MEETING MATERIALS WILL BE EMAILED DIRECTLY TO ALL ACTIVE MEMBERS OF THE HISTIOCYTE SOCIETY BY MARCH 1, 2003.

FOR ALL OTHERS, PLEASE SEND YOUR REQUEST FOR A MEETING PACKAGE TO THE HISTIOCYTE SOCIETY OFFICE OF THE SECRETARIAT IN PITMAN, NEW JERSEY.

Philadelphia Facts

Average temperatures in September ..... 77°F/25°C high
..... 61°F/16°C low

Average precipitation in September ..... 3.88 inches/9.9 mm

City population ..... 1.5 million

Metropolitan area population ..... 6.1 million

Distance from Philadelphia to:

- Antwerp..... 3739 mi/6017 km
- Berlin ..... 4052 mi/6522 km
- London..... 3548 mi/5710 km
- Munich..... 4120 mi/6630 km
- New York City ..... 78 mi/125 km
- Paris ..... 3713 mi/5976 km
- San Francisco..... 2530 mi/4072 km
- Vancouver ..... 2405 mi/3871 km

Most visited historic site ..... The Liberty Bell

Visitor's Information..... www.pcvb.org

Traditional treats ..... Soft pretzels, cheesesteaks, Tastykakes

Personal Data Updates

PLEASE REMEMBER TO KEEP YOUR MAILING ADDRESS, PHONE AND FAX NUMBER, AND EMAIL ADDRESSES UP TO DATE WITH THE OFFICE OF THE SECRETARIAT. IF YOU HAVE ANY CHANGES, PLEASE SUBMIT THEM VIA EMAIL TO **HISTIOSOCIETY@AOL.COM**.

Committee and Study Group Reports

The XVIII Annual Meeting of the Histiocyte Society

was held in Porto, Portugal at Le Meridien Park Atlantic Porto from September 22 to 24, 2002.

83 Medical Professionals attended the meeting. In addition, there were 13 Family Organization Representatives in attendance, for a grand total of 96 meeting participants.

At the time of the meeting the Histiocyte Society had 155 paying members.

The following individuals applied for and were received into Histiocyte Society membership at the Annual General Assembly Business Meeting on the second day of the conference:

Dr. Caterina P. Minniti
Children National Medical Center
Center for Cancer & Blood Disorders
111 Michigan Ave., NW
Washington, DC 20010 USA
Phone: +1 202 884 2887 Fax: +1 202 884 5685
Email: CMinniti@cnmc.org

Dr. Stefaan Van Gool
University Hospital Gasthuisberg
Laboratory of Experimental Immunology
Ped Hemato-Neuro-Oncology, Herestraat 49
Leuven, 3000 BELGIUM
Phone: +32 16 33 22 11 Fax: +32 16 34 38 42
Email: stefaan.vangool@uz.kuleuven.ac.be

Dr. Robert Vassallo
Stabile Building 8-54
200 First Street Southwest
Rochester, MN 55905 USA
Phone: +1 507 266 9728 Fax: +1 507 284 4521

Scientific Committee Meeting Report

Portugal - September 2002

Scientific Committee: Robert Arceci, M.D., Ph.D. (Chair), Thomas Gross, M.D., Ph.D., Jean-Francois Emile, M.D., Bengt Fadeel, M.D., and Marion Schneider, M.D.

HAA GRANT REVIEW OUTCOME

- 19 grant applications were received.
- All were reviewed and comments as well as priority scores were sent to Society Board and to the applicants.
- 8 were funded.

REVIEW OF SOCIETY STUDY OR SPONSORED MANUSCRIPTS

- No manuscripts were sent to the Scientific Committee for review
- Committee recommended a policy of review of manuscripts for the Society as well as review of the same manuscript for journals so as not to allow any conflict of interest and full disclosure.

POSITIVE POINTS AND LESSONS

- We have a consistent system for submission, review and reporting of reviews to help Society and investigators.
- We have established a mechanism for review of manuscripts from the Society.
- We have established a policy of full disclosure for scientific committee members in order to review manuscripts for society and journals.

PROCEDURE OF REVIEW OF GRANTS BY THE SCIENTIFIC COMMITTEE

Members of the committee who have submitted grants of their own must be absent from the discussions of their grant, but should participate in the review and discussion of all other grants, unless there is an evident conflict of interest. An exception to this policy is that the Chairperson of the Scientific Committee is not allowed to submit a grant during their term of office. If there is concern that sufficient numbers of the committee are not able to review a grant, i.e., if more than one person on the committee is recused, or if sufficient expertise on the committee is not present, then appropriate outside reviewers will be requested to participate in the review process.

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The basis for a potential or real conflict of interest, as defined by the NIH, includes the following elements, in part adapted for the purposes of the Histiocytosis Association of America.

EMPLOYMENT: A reviewer who is a salaried employee, whether full- or part-time, of the applicant institution or

continued

COMMITTEE AND STUDY GROUP REPORTS

offeror or who is negotiating with the organization for employment shall generally be considered to have a conflict of interest with regard to applications/proposals from that organization. However, in large organizations or multi-component organizations there may be circumstances where the components are sufficiently independent that an employee of one component can review an application/proposal from another component without a real conflict of interest.

FINANCIAL BENEFIT: (1) Where a reviewer has received or could receive direct financial benefit of any amount, other than from employment, from an applicant institution or offeror or principal investigator related to the application or proposal under review or, (2) where a reviewer has received or could receive a financial benefit that, though clearly unrelated to the application or proposal under review, has a value of $5,000 or more per year, a conflict of interest exists. Regardless of the level of financial involvement, if the individual feels unable to provide objective advice, he/she must recuse him/herself from the review of the application or proposal at issue.

RELATIVES OR ASSOCIATES: A conflict of interest exists if a close relative or professional associate of a reviewer submits an application or proposal, or receives or could receive financial benefits from or provides financial benefits to an applicant or offeror. In such case, it will be treated as the reviewer's financial benefit.

STANDING REVIEW GROUP MEMBERSHIP: When a scientific review group meets regularly, a relationship among the individual members exists; therefore, the group as a whole may not be objective about evaluating the work of one of its members. In such a case, the member's application or proposal will be reviewed by another review group to insure that an objective review is obtained.

REQUEST FOR APPLICATIONS (RFA) OR REQUEST FOR PROPOSALS (RFP): Persons serving as the principal investigator or as one of the key personnel or as a consultant on an application are generally considered to have a conflict of interest with all of the applications or proposals. However, if no other reviewer is available with the expertise necessary to ensure a competent and fair review, a waiver may be granted by the agency head or his/her designee that will permit an individual to review only those applications or proposals with which he/she has no conflict but not those with which he/she has a conflict of interest. No contract may be awarded to an individual who has served as a reviewer of the proposals submitted in response a request for grants nor to that person's close relatives or professional associates or any organization in which the individual had a real financial interest at the time of review.

MULTI-SITE OR MULTI-COMPONENT PROJECT: Persons serving as either the principal investigator, as one of the key personnel, or as a consultant on one component of a multi-site or multi-component project have a conflict of interest with all of the applications or proposals connected with the same project; and, they may have a conflict of interest with other applications or proposals submitted by the principal investigator, other key personnel or consultants of the same project.

LONGSTANDING DISAGREEMENTS: A conflict of interest exists where a potential reviewer has had longstanding scientific or personal differences with an applicant.

APPEARANCE OF CONFLICT OF INTEREST: Where there is an appearance of conflict of interest, but not sufficient grounds for disqualifying the reviewer, the government official in charge of the review will document: (1) that there is no real conflict of interest; and (2) that, at the time of the review, no practical alternative exists for obtaining the necessary scientific advice from the reviewer with the apparent conflict.

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In addition, an explanation of the criteria for review, as described by the NIH (NIH GUIDE, Volume 26, Number 22, June 27, 1997) include:

Scoring Guidelines:
100-150 (outstanding); 151-200 (excellent); 201-250 (very good); 251-350 (good); 351-500 (acceptable)

Some guidelines for each of these categories are listed below:

(1) Significance: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

(2) Approach: Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

(3) Innovation: Does the project employ novel concepts, approaches or method? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

(4) Investigator: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

continued

Committee and Study Group Reports

(5) Environment: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

In addition to the above criteria, in accordance with NIH policy, all applications will also be reviewed with respect to the following:

- The adequacy of plans to include both genders, minorities, and their subgroups as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated.
- The reasonableness of the proposed budget and duration in relation to the proposed research.
- The adequacy of the proposed protection for humans, animals or the environment, to the extent they may be adversely affected by the project proposed in the application.

NEW GRANT PROPOSAL INITIATIVES

- The consideration of funding grants for longer periods of time was tempered by the issue of annual funding available to the Association.
- The alternative of allowing three annual renewals was agreed upon as a potential compromise.
- The idea that possibly one or two grants could be designated for "new" investigators was felt to be something worth considering.

Education Committee Meeting Report

Maurizio Aricò, Chair

1. The committee met in Porto during the Society meeting. Main activity of the committee during the last year was the evaluation of the abstracts submitted for presentation to the Porto meeting.
2. The procedures of evaluation of the abstracts was discussed and the committee decided to send to the Board the suggestion that the committee chairman may have the opportunity to coordinate the evaluation of the abstract. This may serve as the basis for the scientific program of the meeting.
3. The committee may also give suggestions on selection of the invited speakers. All members agreed on that.
4. The committee received from the Board the invitation to draft a standard format for the meeting schedule. The committee accepted to work on this project.
5. After the elections all members of the committee asked the current chairman to serve as the committee chairman for the next term. He accepted.

HLH Study Group Meeting Report

September 2002

Submitted by Jan-Inge Henter, Chair

Members: J-I Henter (Sweden, Chairman), M Aricò (Italy), M Egeler (the Netherlands), G Elinder (Sweden), H Gadner (Austria), S Imashuku (Japan), G Janka (Germany), D Komp (USA), S Ladisch (USA), D Webb (UK). BMT-advisor: A Filipovich (US).

The FHL Study Group is mainly aiming at improving diagnosis and treatment for patients suffering from FHL/HLH. We also want to improve knowledge on the biological mechanisms causing the disease. The HLH-94 treatment protocol has been a therapeutic success. It has also provided a lot of research data, in particular on NK-cell activity in HLH.

1. The HLH-94 protocol is open for new patients. It appears to be effective and appreciated. Most patients registered are from Europe and Japan. The registration in the US/Canada is improving

2. Many patients are being treated in the US/Canada according to the protocol, but the physicians do not report any data to the Study center and this way information which could be useful in further improving the protocol is lost.

3. A report on the outcome of the patients recruited the first four years is has been published (Blood 2002 Oct; 100: 2367-2373).

4. Efforts are also made to summarize the biologic part of the study on NK-cell activity.

5. Although HLH-94 has been considered effective, the Study Group has decided to start the process in developing a new protocol, which will be based on the HLH-94 protocol. The HLH-94 will be open during this process.

PRESIDENTS OF THE HISTIOCYTE SOCIETY

1985 - 1987	**Christian Nezelof**
1987 - 1989	**Blaise Favara**
1989 - 1992	**Stephan Ladisch**
1992 - 1996	**Helmut Gadner**
1996 - 1998	**Göran Elinder**
1998 - 2001	**Kenneth McClain**
2001 - 2003	**R. Maarten Egeler**

COMMITTEE AND STUDY GROUP REPORTS

LCH CNS STUDY GROUP MEETING

Monday, September 23, 2002

Submitted by Nicole Grois

Participants:
R. Arceci, M. Arico, P. Brock, J. Donadieu, R. M. Egeler, H. Gadner, N. Grois, R. Haupt, V. Nanduri, K. McClain, J. Pritchard, H. Prosch, M. Steiner, E. Unger

Patient accrual:
In the LCH study center in Vienna, Austria 1912 patients with LCH are registered on the clinical trials, 219 of these (11%) have hypothalamic pituitary disease with diabetes insipidus (DI) and 31 patients (1.6%) were reported to have "neurodegenerative" (ND) lesions on MRI. This reported incidence seems to be dependent on the observation time and is also center-dependent reflecting the frequency of MR-examination. Of the 31 patients with neuro-degenerative lesions on MRI only 13 have been suffering from neurological deficits, in 12 patients neuro-psychological tests were performed and they were free of symptoms, six patients without overt gross neurological symptoms have not been tested yet. Based on these data, the actual incidence of neurodegenerative CNS LCH might raise over the next years. The clinical significance of MRI findings in so far asymptomatic patients remains to be proven by long-term observation.

Study	Start	Total	MS	DI	Neurodegenerative
		1912	***740***	***219/ 11%***	***31 / 1,6%***
DALHX 83/90	1983	320	63	31/ 10%	8 / 2,5%
LCH I	1990	523	210	63/ 12%	9 / 1,7%
LCH II	1996	901	401	114/ 13%	12/ 1,3%
LCH III	2001	168	66	11/ 6%	2/ 1,6%

524 brain MRIs from LCH patients are available for central review from 181 pts. Based on this imaging material a classification system for the evaluation of cranial and intracranial lesions in LCH will be proposed.

37 patients with CNS LCH were tested according to the guidelines given in the LCH CNS 2000 protocol, 19 patients were neurologically evaluated and 25 patients underwent psychological tests. Electrophysiological tests were performed in 13 patients.

Sera are available in 13 pts, CSF in 7 pts and urine in 15 pts. A central review of 7 brain biopsy specimen done by Prof. Hans Lassmann of the Institute for Brain Research, University of Vienna, Austria revealed prominent CD 8 positive lymphocytic infiltration possibly providing evidence for an autoimmune process in neurodegenerative CNS LCH.

continued

Treatment of CNS LCH:
Patients with tumorous active LCH infiltrates in the cerebral parenchyma or deriving from the meninges seem to benefit from chemotherapy. There are a few anecdotal cases reporting encouraging results with 2-CDA.

So far, 16 patients with neurodegenerative CNS LCH were treated with melatonin as proposed in the LCH CNS 2000 protocol, 5 of these after the official opening of the study. Minimal follow up information was reported in only 13 patients. Only a few patients followed the requirements of the study protocol which included pre- and post treatment evaluation with MRI and neuropsychological assessment. In 11 patients progression of neurological deterioration was reported, in one patient the symptoms remained stable, one patient did not have any neurological symptoms prior to melatonin start and therefore did not meet the entry criteria.

Due to the lack of compliance of the participating patients to the minimal diagnostic requirements of the study and the incomplete data reporting it was decided to close the LCH CNS 2000 protocol in it's current form by December 31, 2002.

Completion of data accrual of the so far registered patients will be attempted. The study group will work out a new LCH CNS protocol including reduced requirements for the diagnostic evaluation and general guidelines for the therapy of the specific groups of CNS LCH.

Information on the efficacy of any treatment given to LCH CNS patients will be collected and evaluated within this study which will open by 1st January 2003.

Committee and Study Group Reports

LCH Study Committee Report

Prof. Dr. H Gadner, Study Chairman
Dr. N. Grois, Dr. M. Minkov, Study Coordinators

Participants: M. Arico, J. Braier, J. Donadieu, H. Gadner, N. Grois, J.-.I. Henter, S. Ladisch, K. McClain, M. Minkov, S. Weitzman, K. Windebank

PROGRESS OF THE LCH III STUDY

THE OFFICIAL START OF THE LCH III STUDY WAS APRIL 1st, 2001. By August 31, 2002, 169 patients have been enrolled in the study, 34 patients were multisystem "RISK" patients, (29 randomizations), and 32 patients were "LOW RISK" patients (21 randomizations). 103 patients were single system patients, of these 27 patients were multi-focal bone patients and 29 patients had single system disease with special site involvement, defined as lesions in the craniofacial bones or skull base with intracranial tumor extension or vertebral lesion with intraspinal extension. No major toxic events or early toxic death have been reported, so far.

To date, the following subcenters are participating in the study:

- The subcenters Argentina, Germany/Austria/ Switzerland/Netherlands, Italy, Scandinavia and USA/ Canada started in April 2002. The subcenters in France started patient accrual in January 2002, in Spain in February 2002 and in the United Kingdom in August 2002.

- Australia, Japan, and Israel applied as new participants and are working on setting up the necessary facilities and organizational requirements. Disappointingly, only a relative small number of follow up reports have been received so far by the statistical reference centre in Vienna, which needs to be improved in order to achieve the study aims in time.

To meet the criteria for IRB approval for all participating centers a Data Safety Monitoring Board (DSMB) was formed in October 2001 and includes Prof. Jacques Otten MD, Belgium, and Prof. David Tubergen MD, U.S.A. as clinicians, Prof. Jörg Michaelis PhD and Andreas Faldum, PhD as external biometrists and Ulrike Pötschger MSc as study statistician. The members of the DSMB (excluding Jörg Michaelis) met together with the study chairman Prof. Helmut Gadner MD at the Annual Meeting in Porto to evaluate the progress of the study. There was the general conclusion that the conduct of the study was appropriate and very consistent with protecting the rights of the patients enrolled in the study, and that the initial patient recruitment and randomization rate was satisfying considering the delayed start of some of the subcenters. To further improve randomisation rate and data recruitment entry for registration, the DSMB proposed to send out a 3-monthly reminder for timely submission of data.

For the next future it is the goal to increase the patient accrual and to improve the randomization rate and to complete the data reporting.

Adult Histiocytosis Study Group Report

Submitted by Maurizio Aricò, Chair

The study group met in Porto in an open session.

The final evaluation of the retrospective study on 274 adult LCH patients was discussed. The resulting manuscript will thus be submitted to the Scientific Committee of the Society for approval before submission for publication.

On the basis of the experience made with the retrospective study, the groups has worked during the last two years for the preparation of the first international therapeutic trial for LCH in adults.

This was discussed in the committee with the help of some outstanding pulmonologists. It was agreed that in this study all patients, diagnosed and evaluated according to the recent society standards, will be stratified into 3 groups: single system, multisystem, and pulmonary isolated LCH.

The treatment of SS and MS LCH will be the standard chemotherapy regimen developed in children by the Society. For the peculiar pulmonary isolated disease, the study is aimed at the definition of the natural history of the disease, so that patients will be treated only upon disease progression. This will allow us to describe for the first time the natural course of pulmonary isolated LCH in adults, with particular interest on the role of cigarette smoke.

The draft of the therapeutic protocol will be circulated among the study committee until all the details will be defined.

Hopefully, the trial could be open to patients accrual within 6 months.

continued

Committee and Study Group Reports

LCH Late Effects Study Group and Epidemiology Study Group Reports

Submitted by Riccardo Haupt (LESG), and Stacy Nicholson, Chairs

Participants:
C. Bernstarnd, J Braier, J. Donadieu, R. Haupt, V. Nanduri, H.S. Nicholson, R. Jubran, S. Weitzmann

The two Study Groups met together at the annual meeting in Porto, and the topics of discussion were:

Endocrine follow-up study proposal: After the conclusion of the previous retrospective study on prevalence of permanent consequences among LCH long-term survivors, it has been decided that the Group should focus on more precise end-points. In particular, after a proposal by Vasanta Nanduri, Nicole Grois, and Riccardo Haupt, it has been decided to start a specific endocrine study on DAL, LCH-LESG, and French patients. The committee will meet again in late November and a proposal will then circulate. Regarding this topic, the group also underlined that would like to be involved in the endocrine follow-up of LCH I, II & III patients.

LCH-Malignancy Registry So far, 71 pediatric cases of the association LCH and malignancy have been registered. Four new cases have been reported but not yet registered. Data on leukemias were presented at the meeting, and those on solid tumors discussed within the Group. Some associations seem of interest. In particular, T-ALL, APL, retinoblastoma and neuroblastoma seem to be more frequently reported. Dr. Haupt, who has the responsibility of the Registry, will circulate a letter among physicians who treated these patients to check for availability of biological material. Specific study proposals will be presented by the French group regarding APL, and by the Italian group for ALL.

LCH and ethnicity Dr. Rima Jubrhan, reported an her observation of an apparently high prevalence of subjects with a Latino origin within the LCH population followed at the Los Angeles Children's Hospital. She has proposed an epidemiological study focused on possible environmental exposures. It was discussed to possibly extend this study to other countries in Central and South America.

Epidemiology of LCH in UK: Dr. Vasanta Nanduri reported on an ongoing project in the UK that will allow to contact GP and pediatricians of the NHS in order to collect information on LCH cases among their patients. This will allow the development of a general etiological study.

LCH -Salvage Committee Meeting Report

Submitted by Sheila Weitzman, Chair

Sept 2002

The Salvage Committee met twice during the Histiocyte Society meeting. The first order of business was the presentation of the updated results of the open salvage protocol LCH-S-98.

As of the most recent update from Vienna, 71 patients had been registered on study, as expected the majority – 69% were patients who failed LCH-II. 47 (79%) had risk organ involvement at diagnosis, but follow up data is available only on 41. 24 patients were without risk organ involvement at diagnosis, many patients are still missing significant amounts of data.

The accrual to LCH-S-98 in stratum one (risk patients who had been previously registered on LCH-II or LCH-III) has been reasonably good---47 of the 60 patients required by the study have been accrued to date.

Although the registrations of patients in stratum 2 has improved over the last year, it is apparent that accrual to stratum 2 will be inadequate for evaluation within a reasonable time period. With the 24 non-risk patients registered on stratum 3, together with 10 further patients registered directly with Toronto (since the decision a year ago that Vienna would follow only those patients with prior registration on LCH-II and III), it is possible that meaningful results will be obtained in this stratum as well as stratum 1

In order for the results of this study to be evaluable, the part time Clinical Research Associate(CRA) at the Hospital for Sick Children(HSC), Canada (funded by the Histiocyte Association of Canada), will obtain from the study center in Vienna, the names of the physicians caring for patients with missing data, and will contact them to try to obtain the necessary follow up data.

With this it is hoped that sufficient data at least in strata 1 and 3 will be available by the time the next study is ready to open(see below). LCH-S –98 will therefore close to patient accrual at that time.

The group next discussed the follow up studies.

continued

COMMITTEE AND STUDY GROUP REPORTS

Proposed study for low risk patients with chronically reactivating LCH:

The group first discussed a new study for low risk patients:

a) Risk patients who respond well to LCH-II or LCH-III but who reactivate in non-risk organs, or

b) Patients with low risk disease form the onset but who reactivate following therapy as per LCH-II or LCH-III.

It was felt that as many patients reactivate only once, the protocol should be limited to patients with a second or subsequent reactivation. Because of the available suggestive evidence that 52 weeks of therapy may be better than 26 weeks , it was decided that therapy should continue for a total of 52 weeks for all patients.

In order to try to answer the question of whether 2-CdA decreases the number of subsequent reactivations it was felt that the patients should be randomized at registration to either:

1) Vinblastine weekly for 6 weeks together with oral prednisone, or

2) Cladribine (2-CdA) given for 2 courses of 5 days each

The patients would all be evaluated for response at 6 weeks.

Following the good results and minimal toxicity of the protocol presented by Dr Henter, with daily oral 6 mercapto purine and weekly oral methotrexate, it was decided that the maintenance part of the protocol should consist of these drugs given until the end of 52 weeks of therapy.

All patients, except those with clearly progressive disease at 6 weeks, would go onto the oral 6MP and Methotrexate maintenance outlined above following the randomized induction therapy.

It was felt that there were insufficient numbers for a second randomization to 1 vs 2 years of maintenance, although this may be something to be considered in a future study.

Dr Milen Minkov from Vienna agreed to put together a study proposal which will be submitted as soon as possible to the board and the scientific Committee for approval.

It was suggested by Dr Weitzman that the board should consider having study committees follow the COG model, with a mixture of young investigators and more experienced investigators to act a mentors. The various study centers could then be asked to nominate a young investigator from whom that section of the study committee could be chosen. This may help to encourage accrual from non-European centers.

Proposed salvage study for Risk Patients who fail to respond to the LCH-III protocol at 6 or 12 weeks or who reactivate in risk organs

Two findings underlie this proposal:

1) It has been previously shown that "Risk" patients who fail to respond to up front therapy by 6 weeks (2 drugs) or 12 weeks (3 drugs) have a high mortality.

2) It appears from evaluation of the LCH-S -98 results that risk patients who fail to respond to 2-CdA salvage therapy have a very high risk of dying.

Review of the literature on stem cell transplant suggests that this may be a curative option for these patients, if the patients survive the transplant procedure. It was generally felt that in view of the known poor outlook of this group of patients, that they should be referred for transplant as soon as a compatible donor is available. The group was reminded by Dr Grois that all risk patients registered on LCH-III and their immediate family members should have HLA typing done at the time of initial registration.

For all patients failing to respond to LCH-III therapy at 6 weeks who do not have a compatible family donor, a computer search should be instigated at that time.

The patients should proceed on therapy as per LCH-III and either move to LCH-S-98 immediately or after another attempt at induction. According to the recent update of LCH-S, those responding to LCH-S-98 should continue on 2-CdA (maximum of 6 courses). Unless the updated follow up changes the data, patients who responded to 2-CdA had a very low mortality and therefore should not be referred for transplantation.

However those not responding to 2-CdA should go onto other salvage therapy, possibly 2-CdA/ARA -C or a TNF receptor inhibitor) and onto stem cell transplant as soon as possible.

Drs. Egeler and Filipovich and the transplant group will submit this concept for presentation to the Histiocyte Society board and the Scientific Committee.

In the meantime, an addendum to LCH-III with regard to a donor search for poor responders should be submitted as soon as possible. Once again a study committee for the transplant protocol remains to be finalized.

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