

# Treatment of Langerhans Cell Histiocytosis – Evolution and Current Approaches

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**Summary** Optimal treatment of Langerhans cell histiocytosis remains problematic. The absence of controlled studies and the lack of standard diagnostic and evaluation criteria have impeded therapeutic progress even though knowledge of basic aspects of LCH have advanced. Historical analysis of outcome suggests little improvement until very recently, but marked differences in outcome according to extent of disease. Consequently, major and now successful efforts have been made to stratify LCH patients into different 'risk groups'. Recent findings suggest that combination chemotherapy for multisystem disease is beneficial and that VP-16 is a useful new agent for treating LCH, despite controversies regarding its side effects. The first randomised international treatment study, LCH-1, being conducted by the Histiocyte Society, should resolve some of these controversies. Other experimental therapies may be considered for children with severe, unresponsive LCH.

## Background

The treatment of Langerhans cell histiocytosis (LCH) has varied greatly over the past century, and is still controversial. To some extent, treatment reflected early views on disease pathogenesis, i.e. granulomatous, inflammatory, or infectious. Consequently children with LCH were treated with antibiotics, with anti-inflammatory agents including steroids, with radiation therapy, and, over the last 20–30 years, with cytotoxic chemotherapy. While varying degrees of success have been reported, it should be evident that only once the issues of aetiology and pathogenesis have been resolved can a definitive therapy be envisioned. Nevertheless, systematic approaches to diagnosis and treatment, which were major advances of the 1980's, have improved the outlook for children with LCH and are the main subject of this paper.

## Historical perspective

The first systematic treatment trial of children with LCH was that of Lahey (Lahey, 1962). In this study children were matched for age and degree of disease and outcome was analyzed according to whether or not "specific" treatment for LCH was given. However, treatment was not controlled, and included various agents including antibiotics, steroids, and cytotoxic agents. The principal conclusion of this study was a significant increase in survival in the group of children receiving therapy compared to those who were untreated.

These findings led to a number of studies in which, unfortunately, the patient populations varied greatly with respect to extent of disease. This variability made interpretation of results difficult, and conclusions regarding superior treatment approaches at best tenuous. Consequently, to obtain an overview of the status of treatment of LCH at a time at which it appeared some progress was being made, survival data of a number of studies were analyzed (Ladisch, 1983). The analysis included nine treatment studies with 433 patients, with an overall long-term survival rate of 71%. When patients with monostotic eosinophilic granuloma, generally a self-limited process with no mortality, were excluded, there were 391 patients with multifocal or multisystem disease. The majority of these patients could be classified into 3 groups (B, C, and D in Table 1), according to increasing extent of

**Table 1** Survival in LCH

	Survival (%)			
	A	B	C	D
Oberman (1961)	61	95	44	33
Avery <i>et al.</i> (1957)	81	100	86	0
Daneshbod <i>et al.</i> (1978)	82	–	100	0
Nezelof <i>et al.</i> (1979)	52	–	59	38
Komp <i>et al.</i> (1980)	78	100	91	54
Lahey (1975)	71	–	98	33
Toogood <i>et al.</i> (1979)	80	100	90	40
Lahey <i>et al.</i> (1979)	68	100	68	–
Komp <i>et al.</i> (1977)	72	100	91	54
Total % survival	71	98	76	37

A = all LCH excluding monostotic eosinophilic granuloma; B = "mild" multifocal eosinophilic granuloma; C = soft tissue involvement (i.e. multisystem), but without organ dysfunction; D = multisystem disease with organ dysfunction.

disease. The outcomes of the 9 studies are listed in chronological order, and they span the period from before 1950 to the end of the 1970's.

Outcome was clearly related to extent and severity (presence or absence of organ dysfunction) of disease at diagnosis and demonstrates the need to stratify patients prior to analyzing outcome or response to treatment. Mortality is clearly highest in patients with organ dysfunction. A disappointing conclusion from this analysis, however, is that survival during the previous half-century had not obviously improved (% survival, reading down the columns). This was particularly evident in group D. Therefore, careful stratification of patients, and ultimately randomization of patients, is essential to avoid drawing erroneous conclusions about treatment efficacy which could result from differences in the relative severity of patients enrolled in one study versus another. The importance of stratification for the purpose of analysis, was finally recognised and implemented in studies initiated in the last decade (1980's), which are now discussed in detail.

## Basic issues

Ignorance of the pathogenesis of LCH and the previous failure to establish commonly agreed diagnostic and stratification criteria were challenges for the 1980's. It had become generally accepted that therapy should depend on classifying patients as to whether they had single or multisystem disease. Furthermore, there was recognition of the

importance of the number of organs and systems involved on morbidity and prognosis, especially in young patients with multisystem disease and organ dysfunction at time of diagnosis. Finally, chemotherapy including cytostatic agents had been shown to exert a beneficial, although not definitely proven, effect. No single drug or regimen, however, has been demonstrated to unequivocally influence the unpredictable course (associated with a high mortality rate) in severely affected children. Therefore, there has been an ongoing search for new systematic and prospective therapeutic approaches, using new agents as well as widely used and reasonably effective drugs such as vinblastine.

In a rare disease with highly variable clinical presentation, it is crucial to use uniform clinical and histopathological criteria for diagnosis and for assessment of disease extent. For this reason efforts have been made to establish generally accepted staging and standard classification systems. Previously, patients usually were staged into localized and disseminated LCH, depending on clinical criteria. Localized disease consisted of isolated bone, lymph node or skin involvement. Disseminated disease was defined as the presence of multiple LCH lesions of any other type or combination. Using a modification (Ladisch, 1983) of a previously suggested stratification scheme (Oberman, 1961), patients with disseminated disease treated in single institutions (Raney *et al.*, 1989) or included in cooperative studies (Ceci *et al.*, 1993; Feldges, 1981; Gadner *et al.*, 1994) were categorized into different risk groups. Patients with multifocal bone involvement were distinguished from those with bone and soft tissue or solitary soft tissue involvement and those with dysfunction of the liver, lungs and/or hematopoietic system were categorised separately. Finally, the writing group of the Histiocyte Society developed a new classification system of the histiocytic syndromes in children, and proposed a uniform approach to diagnosis. The system includes specific histopathological criteria and a patient stratification based on standardized diagnostic evaluations of the extent of the disease (Histiocyte Society Writing Group, 1987; Broadbent *et al.*, 1989).

Prior to considering treatment approaches specifically, a remaining issue is that of definition of response. In a disease in which spontaneous regression is possible, and a chronic or relapsing course is not infrequent, a new definition and assessment of response to a given treatment had to be established. This contrasts to a malignant process, in which the aim of therapy is the eradication of a malignant clone, which is then followed by cure of the disease. In a reactive disease process, the definition of response must be adapted. Currently, with respect to LCH, response is defined as a measurable resolution of symptoms and signs and the prevention of permanent consequences of the disease.

### Principles of current therapy

#### Single system disease

The clinical course of LCH in patients with single system disease (usually bone, lymph node or skin) is generally benign, with a high chance of spontaneous remission and favorable outcome over a period of months to years (McLelland *et al.*, 1990). Despite lack of knowledge regarding the etiology of LCH, some therapeutic principles have emerged from clinical experience. Bony lesions usually do not require treatment other than biopsy, necessary to confirm diagnosis, or curettage at the time of initial biopsy. Further local therapy is recommended only if weight bearing bones (with a risk of spontaneous fracture) are involved, or lesions cause pain or could result in unacceptable dysfunction or deformity. Intralesional infiltration of steroids (40–200 mg methylprednisolone) recently has also been reported to be an effective and safe treatment modality (Egeler *et al.*, 1993). By contrast, the use of radiation therapy in the management of localized bony or soft tissue disease (Gramatovici *et al.*, 1988; Selch *et al.*, 1990) has decreased considerably, possibly because of better understanding of the natural history of this

form of disease (resolution), as well as the 5% risk of second tumor development (Greenberger *et al.*, 1981). However, under circumstances when the consequences of the disease threaten the function of a critical organ (e.g. lesions surrounding optic nerve or spinal cord) and local infiltration of corticosteroids is not feasible, emergent treatment with low dose radiotherapy (6–10 Gy) is warranted.

For isolated lymph node infiltration or isolated nodular skin lesions, surgical excision undoubtedly is the therapy of choice, provided that generalized disease is excluded. Patients with disseminated single system skin disease present a particular problem. Whereas mild involvement may respond to topical steroid treatment, in the case of severe symptomatic skin disease with widespread areas of crusting and excoriation, topical application of a 20% solution of nitrogen mustard has been shown to be effective. Sheehan *et al.* (Sheehan *et al.*, 1991) reported a rapid clinical improvement in 16 children within 10 days, with subsequent complete healing observed in 14 cases and partial response in 2. Disseminated skin lesions may also be controlled by PUVA photochemotherapy (Neumann *et al.*, 1988). Both of these treatment approaches, however, can be recommended only for short term therapy, as there is concern that in the long term they carry with them the possibility of carcinogenicity.

#### Multi-system disease

Lack of understanding of the pathogenesis of LCH and the heterogeneity of clinical presentation not only impeded the adoption of a generally accepted clinical and histopathological staging and classification system, but also the adoption of a rational treatment policy. Major obstacles were the changing belief that LCH is a reactive rather than a malignant process and the inability to identify prognostic factors which could predict outcome (Berry *et al.*, 1986). This explains why treatment of a disease which may be acute, subacute, or chronic as well as progressive, stable, or sometimes spontaneously regressing, becomes controversial (Broadbent *et al.*, 1985). Two major approaches exist; a "conservative" approach using minimal therapy, and an intensive chemotherapy treatment plan.

Based upon observation of spontaneous remission which may occur in the course of multi-system disease (Broadbent *et al.*, 1984), the approach of minimal intervention has been adopted by several institutions (Raney *et al.*, 1989; Broadbent *et al.*, 1985). Only in cases with evidence of fever, pain, immobility, failure to thrive or worsening disease in vital organs was a pulsed dose of prednisolone (60 mg/m<sup>2</sup>/day) given for a short period, followed then by cytostatic drugs (vincristine or vinblastine, etoposide (VP-16) only in the case of disease progression. Eight of 44 patients with multi-system disease did not require systemic therapy and in 17 prednisolone alone was effective. Overall survival was 82% (18% mortality) and survival was 64% in children with organ dysfunction. However, 24 of 36 survivors had some permanent consequences, and diabetes insipidus occurred in 36% of patients with multi-system disease. These results (McLelland *et al.*, 1990) clearly differ from the data published by the Italian and German cooperative chemotherapy study groups, which used an intensive chemotherapeutic approach (below). These two groups prospectively evaluated the impact of rapid initiation of rather intensive chemotherapy, but specifically in patients with disseminated disease, thus beginning to apply the principle of stratification discussed earlier.

The Italian multicentre AIEOP-CNR-HX 83 Study prospectively tested the outcome of patients stratified into good and poor prognostic groups according to the absence or presence of organ dysfunction at the time of diagnosis (Ceci *et al.*, 1993). The treatment of the good prognosis group consisted of the sequential use of single agents to obtain response. These agents were vinblastine (6.5 mg/m<sup>2</sup> i.v. weekly for 3 months) followed by doxorubicin (20 mg/m<sup>2</sup> i.v. for 2 consecutive days every 3 weeks for 3 months), and finally VP-16 (200 mg/m<sup>2</sup> i.v. for 3 consecutive days 3 weekly for at least 3 months). The poor risk group received nine

courses of a 4 week treatment with combination chemotherapy including vincristine, cyclophosphamide, doxorubicin and prednisone. After an observation time of 4 years 92% of 84 valuable patients were alive. The complete response rate after the different monotherapy periods was 63% with vinblastine, 43% with doxorubicin and 88% with VP-16, suggesting special efficacy of VP-16. However, only 2 out of 11 poor risk patients (18%) had a complete resolution of disease, while 6 died and 7 still suffered from chronic disease. Disease-related permanent consequences were encountered in 48% of all patients with an incidence of diabetes insipidus of 20%. These data emphasize that monochemotherapy is very effective in good prognosis patients, but even more aggressive polychemotherapy does not improve the outcome in patients with bad prognostic features at diagnosis.

The Deutsche Arbeitsgemeinschaft für Leukaemieforschung (DAL), in a multi-center clinical trial, prospectively tested the hypothesis that in disseminated LCH relatively intensive chemotherapy (without alkylating agents and anthracyclines), initiated soon after diagnosis, followed by a long-term continuation therapy, would rapidly decrease disease activity, reduce mortality, and prevent recurrences and chronic disease (Gadner *et al.*, 1994). One hundred and six newly diagnosed patients stratified into 3 risk groups (group A: multifocal bone, group B: soft tissue involvement without organ dysfunction and group C: with organ dysfunction) received an identical initial 6 week treatment with prednisone, vinblastine and VP-16, and risk-adapted continuation treatment of one year's duration including oral 6-mercaptopurine and 8 pulses of vinblastine and prednisone for all patients, plus VP-16 in group B and VP-16 and methotrexate in group C. The majority of patients achieved complete resolution of disease (89% in group A, 91% in group B and 67% of the most severely affected patients in group C). The speed of resolution was rapid (median 4 months) and independent of extent of disease. Recurrence after initial resolution was seen only infrequently during a median follow-up of 6 years and 9 months (12%, 23% and 42% in groups A, B, and C). Finally, mortality was low (overall 9%, 38% in group C). These results contradict the widespread wisdom, derived from the reported high incidence of recurrences (of up to 65%), that treatment of LCH with chemotherapy will neither influence the natural course of disease nor prevent the high rate of deaths in severely affected patients (46 to 67% in the literature) (Ladisch, 1983; Raney *et al.*, 1989; McClelland *et al.*, 1990; Selch *et al.*, 1990; Mathus-Ridley *et al.*, 1983).

Another important finding in this study was that permanent consequences as a direct result of the primary disease were seen in only 20% of patients after initiation of therapy (Gadner *et al.*, 1994), in contrast to a previously reported incidence of permanent consequences of more than 50% in LCH (Komp, 1981). Strikingly, diabetes insipidus occurred in 10% of patients after initiation of treatment, which is much less than the up to 50% incidence which has been previously observed (Grois *et al.*, 1994). Overall, these results suggest that the rapid initiation of therapy may be reducing the incidence of disease-related permanent consequences.

Another possibly effective multi-agent regimen for multi-system disease was recently published by Egeler *et al.* (Egeler *et al.*, 1993). It includes cytosine arabinoside (100 mg/m<sup>2</sup> s.c. daily for 4 consecutive days), vincristine (1.5 mg/m<sup>2</sup> i.v. given only on the first day), repeated 9 times every 4–6 weeks, and prednisone (initially for 4 weeks at 40 mg/m<sup>2</sup> daily p.o., followed by 20 mg/m<sup>2</sup> daily) for a whole year. Eight of 10 patients without organ dysfunction and 5 of 8 cases with organ dysfunction at diagnosis showed complete resolution of disease after an observation period between 3 and 12 years. The overall incidence of diabetes insipidus in this group of patients was 4 of 18 (22%). Although the numbers of patients treated is still small, and more patient accrual will be required to reach definitive conclusions, the results compare satisfactorily with other therapeutic regimens and has the advantage of causing only mild toxicity.

Recent evidence has shown that VP-16, a semisynthetic

epipodophyllotoxin derivative, is effective in a wide variety of human malignancies, including neoplastic disorders of the monocyte/macrophage lineage, as well as in LCH. Fifteen of 18 children (83%) with recurrent LCH resistant to standard therapy in an Italian series demonstrated clear disease regression with VP-16 therapy (200 mg/m<sup>2</sup> given on 3 consecutive days every 3 weeks). After a median follow up of 12 months there were only 2 documented recurrences amongst a total of 12 patients with initial complete resolution (Ceci *et al.*, 1988). Similar good responses were reported by Broadbent *et al.* (Broadbent *et al.*, 1989) who treated 10 patients with severe steroid-resistant multi-system LCH with 3 weekly courses of VP-16 given for 3 days (150 mg/m<sup>2</sup> over 4 hours or 300 mg/m<sup>2</sup> orally). Nine of 10 children showed definite clinical response after the first or second course of VP-16, suggesting VP-16 as possible component of "first line" therapy for LCH in infancy and childhood. In a further publication by Viana (Viana *et al.*, 1991) 6 previously untreated children with multisystem disease, most of them under 2 years old, received VP-16 (150 mg/m<sup>2</sup> i.v. on 3 consecutive days at 3–4 weekly intervals). Five patients responded completely. Overall, the findings indicate that VP-16 is an effective agent. Consequently, it is now commonly used in the treatment of LCH.

There is, however, some concern about the use of VP-16 in LCH. This concern originates from the observation of an apparently increased risk of secondary leukemia in patients treated with chemotherapy for various malignancies, in which VP-16 was one of the therapy elements. More recent analysis suggests, however, that the risk may have been overestimated (Hawkins *et al.*, 1992). Experience of members of the Histiocyte Society indicates that the incidence of secondary leukemia in VP-16 treated LCH patients is about 1% (Ladisch *et al.*, 1994). VP-16 is one of the most effective current treatments for LCH, a disease which may have a fatal course. The risk:benefit ratio must be firmly established so that its true role can be defined.

#### Experimental therapeutic approaches

Experimental therapy is comprised of either the randomized selection of potentially comparable treatment approaches, or the use of experimental new agents and approaches. This last decade of the twentieth century will be marked by the application of both these approaches to the treatment of LCH. The first of these is randomization of patients, and is the basis for the first international study of LCH, by the Histiocyte Society.

#### LCH-1

Since the most effective treatment approach for LCH has yet to be established, in April 1991 the Histiocyte Society initiated the first international study (LCH-1). Only newly diagnosed, previously untreated patients up to the age of 18 years with multi-system disease and a definitive diagnosis of LCH are eligible for the study. The study requirements include the confirmation of diagnosis according to defined histopathological criteria (Histiocyte Society Writing Group, 1987), a uniform patient stratification based on standardized diagnostic assessments of disease extent (Broadbent *et al.*, 1989), and central data collection and recording.

The aims of the study are: i) to conduct a prospective test of the role of chemotherapy started as soon as possible after confirmation of diagnosis, and ii) to achieve a randomised comparison of 2 commonly-used treatments with respect to response, rates of failure and assessment of toxicity and/or late sequelae. For this purpose, a clear definition of the disease state (active or inactive disease) and response criteria were established. Regular evaluations are performed at fixed intervals (after 2, 4, and 8 courses of therapy).

All patients with multi-system disease are randomly assigned to receive either VP-16 (150 mg/m<sup>2</sup> i.v. over 2 hours) given on 3 consecutive days every 3 weeks or vinblastine

(6 mg/m<sup>2</sup> i.v. bolus) weekly for a period of 24 weeks. Initially there is a single pulse of high dose methylprednisolone (HDMP) therapy in an attempt to achieve a prompt improvement of general symptoms (i.e. fever, dyspnea, pain etc.) but, thereafter, vinblastine or etoposide are given alone. The chemotherapy protocol was designed to maximise the chance of rapid control of disease activity to prevent possible progression, to reduce mortality, and to lessen the incidence of recurrences and late sequelae.

By September, 1993, 242 patients had been registered. One hundred and ten of the registered patients had multisystem disease at diagnosis and 79 (38 males, 41 females) were randomized for treatment (90% with a confirmed 'definitive' diagnosis). The median age of randomized patients with multi-system disease was 18 months (range 6 days - 14 years 6 months). Remarkably, the median interval from onset of symptoms to diagnosis was only 3 months and the therapy started at a median of 8 days from diagnosis. After a median observation time of 17 months (range 4-30 months) 54 of the 79 randomized patients could be evaluated with respect to response after 2 courses (6 weeks) of therapy. At that point 10 had progressive disease, 21 had intermediate response (stable or mixed response) and 23 were improved.

Patients who showed a clear response after 2 courses (6 weeks) clearly benefitted from treatment. Fifteen of 20 children on whom complete data were available after completion of the protocol therapy (24 weeks) had a complete resolution of symptoms and signs. Three more were improved, and only 2 still had intermediately active disease. Preliminary data regarding the efficacy of changing therapy (when response has not been achieved by one arm of the protocol) is beginning to accrue: 24 of 79 patients included in the study were switched to the alternative therapy arm at different intervals, according to the recommendation of the study protocol. Only 5 of these 24 patients improved after the change of therapy, and all 5 had been 'switched' relatively 'late' i.e. after at least 12 weeks of treatment. In contrast, of 7 patients who were 'switched' early i.e. during the first 6 weeks (2 courses of therapy) because of nonresponse, 6 patients suffered progressive disease and 4 of them died. Studying the outcome of all 10 patients categorized as being 'worse' after 2 courses of therapy, a total of 6 (including the 4 patients who had been switched to other therapy) died and only 1 survivor showed a clinical improvement, in the sense of a "better" response to the other single agent. Overall, 10 children died because of nonresponse and disease progression during the observation period. With the exception of one patient with a transient improvement, none of them had achieved a "better" response after 2 courses of therapy (6 of them were nonresponders "worse" and 3 "intermediate complicated", and one "better"). The median interval from diagnosis to death was 8 months (range 3-22 months). All were less than 2 years old (median 13 months) and had liver and spleen involvement. These preliminary findings again point to the importance of response to rapidly instituted initial therapy.

Although this study has not yet been completed, the preliminary data can be summarized as follows: treatment used in the LCH-1 study can be expected to result in regression of the disease within 6 to 12 weeks (2 to 4 courses) in about 50% of patients. The speed of initial response may be important in prognosis. The most severely ill children i.e. those under 2 years of age with multi-system disease and multiple organ involvement (including liver and spleen) who were switched to the alternative therapy arm (or to other salvage chemotherapy) after an initial nonresponse hardly benefitted. The findings of LCH-1, to date, confirm that children with severe multisystem disease who are unresponsive to initial therapy can be considered candidates for experimental approaches.

#### Other therapies

Only preliminary data exist on the efficacy of alternative treatment approaches in multi-system disease. There is no convincing evidence that thymic hormones or thymic factors,

first studied by Osband *et al.* (Osband *et al.*, 1981) are effective in controlling the disease in unselected patients. They reported successful treatment of 10 of 17 patients with multisystem disease (12 of them had a suppressor cell deficiency) with crude extract of calf thymus gland injected daily intramuscularly. Because treatment was associated with an improvement in symptoms and correction of the immunological abnormalities, these findings led to a broader use of thymic hormones or their derivatives such as thymostimulin, thymopentin (Davies *et al.*, 1983; Eckstein *et al.*, 1985) or crude calf thymic extract (Ceci *et al.*, 1988) in several studies. The inconsistent findings regarding the lymphoid cell pattern (NK-cell deficiency, low number of T-suppressor cells or T-helper cell reduction) in individual patients and the variable response to treatment suggested a broad heterogeneity of the immunological abnormalities in LCH. These overall disappointing results did not justify the further application of this treatment in LCH.

Small studies of alpha-interferon (IFN-alpha), given in a daily injection of 1-3 (or more) million U/m<sup>2</sup> i.v. or s.c., have been carried out, especially in patients with frequent recurrences of multi-system LCH, in an attempt to increase NK cytotoxic activity. Although the first reports showed a successful modulation of LCH in two monozygotic twin-brothers (Jakobson *et al.*, 1987) and other patients (Bellmunt *et al.*, 1992), not all patients respond and prospective clinical trials would be necessary to establish the therapeutic value of this agent. However, a clinical trial of recombinant human IFN-alpha in LCH, initiated by the Pediatric Oncology Group, has been discontinued (Halton *et al.*, 1992).

Recent studies suggest a possible role for cyclosporin A (CSA) therapy in young children with advanced multi-system disease. The rationale for using CSA arises from its immunosuppressive and immunomodulatory effects, by selective inhibition of the cellular immune response and cytokine-mediated cellular activation. In Mahmoud's *et al.* original description of the use of CSA in LCH (Mahmoud *et al.*, 1991) all 3 newly diagnosed, previously untreated patients had resolution of organ dysfunction and regression of most lesions. Complete response, however, was attained only by adding steroids and/or vinblastine. Further single institution experiences have been collected by members of the Histiocyte Society (Arico, 1991; Mahmoud *et al.*, 1993) in a retrospective survey of 18 patients with multisystem disease treated with CSA with or without other relatively non-toxic agents (i.e. prednisone and vinblastine) in Europe and the United States; 12 children died (Mahmoud *et al.*, 1993). Further trials will clearly be required to establish the potential value of CSA.

Few data are available regarding the role of bone marrow-ablative therapy with bone marrow transplantation (BMT) in recurrent multi-system disease (Morgan this issue). The first successful allogeneic engraftments with subsequent cure of the disease were published by Ringden in 1987 (Ringden *et al.*, 1987) and Stoll in 1990 (Stoll *et al.*, 1990). Recently, the Seattle group reported another 4 patients successfully treated with stem cell infusion. All 6 patients were conditioned with high dose chemotherapy and total body irradiation. Overall, 4 received an allogeneic and 2 an autologous graft. Only 2 of these patients (a 1.5 year old girl 820 days after allogeneic engraftment and a 45 year old patient 1620 days after autologous stem cell infusion) are disease-free survivors. One patient died 355 days after allogeneic BMT because of disease recurrence and a 15 year old female died 14 days after autologous infusion due to toxicity (Greinix *et al.*, 1992). Certainly this approach, especially the rationale for autologous engraftment, needs to be reviewed (Morgan this issue).

To return to the analysis of LCH-1 data, the study has revealed that a small group of patients with a high risk of a poor outcome can be identified very early in their course, after only 6 weeks of treatment. This group includes a subset of patients suffering of a form of disease with an 80% probability of early death, despite other chemotherapeutic approaches. For these patients the Histiocyte Society has established a Salvage Therapy Group to propose a study for

the use of experimental treatment approaches, rather than continuing the apparently unsuccessful chemotherapeutic regimens used to date.

This treatment is described in detail in the LCH-1-S protocol of the Histiocyte Society and comprises a choice of (a) high dose immunosuppressive therapy (combination of CSA and antithymocyte globulin (see Kannourakis and Abbas, this volume), or (b) marrow-ablative therapy with allogeneic bone marrow transplantation (Morgan this issue). The protocol, now open for enrollment, is considered a continuation of the systematic study of LCH by the Histiocyte Society and its members, and will be open for those patients who have been

initially treated on the LCH-1 protocol.

In conclusion, several advances in the management of LCH have been made, but substantial progress is still required to achieve a higher cure rate. Major advances of recent years include (a) a systematic approach to the diagnosis of LCH, (b) stratification of patients according to disease severity, (c) development of criteria for response and (d) the institution of the first randomized and international cooperative treatment trial. The results of ongoing studies should lead to an even better outcome for patients with LCH in the near future.

## References

- ARICO, M. (1991). Cyclosporine therapy for refractory Langerhans cell histiocytosis. *Blood*, **78**, 3107.
- AVERY, M.E., MCAFFEE, J.G. & GIULD, J.G. (1957). The course and prognosis of reticuloendotheliosis (eosinophilic granuloma, Schuller-Christian disease and Letterer Siwe disease): a study of 40 cases. *Am. J. Med.*, **22**, 636-642.
- BELLMUNT, J., ALBANELL, J., SALUD, A., ESPANOL, T., MORALES, S. & SOLE-CALVO, L.A. (1992). Interferon and disseminated Langerhans cell histiocytosis. *Med. Ped. Oncol.*, **20**, 336-337.
- BERRY, D.H., GRESIK, M.V., HUMPHREY, B., STARLING, K., VIETTI, T., BOYETT, S. & MARCUS, R. (1986). Natural history of histiocytosis X: a Pediatric Oncology Group Study. *Med. Ped. Oncol.*, **14**, 1-5.
- BROADBENT, V., PRITCHARD, J., DAVIES, E.G., LEVINSKY, R.J., HEAF, D., ATHERTON, D.J., PINCOTT, J.R. & TUCKER, S. (1984). Spontaneous remission of multi-system Histiocytosis X. *Lancet*, **4**, 253-259.
- BROADBENT, V. & PRITCHARD, J. (1985). Histiocytosis X -current controversies. *Arch. Dis. Child.*, **60**, 605-607.
- BROADBENT, V., PRITCHARD, J. & YEOMANS E. (1989). Etoposide (VP16) in the treatment of multisystem Langerhans cell histiocytosis (Histiocytosis X). *Med. Ped. Oncol.*, **17**, 97-100.
- BROADBENT, V., GADNER, H., KOMP, D. & LADISCH, S. (1989). Histiocytosis syndromes in children II. Approach to the clinical and laboratory evaluation of children with Langerhans-cell histiocytosis. *Med. Ped. Onc.*, **17**, 492-495.
- CECI, A., DE TERLIZZI, M., COLLELA, R., BALDUCCI, D., TAMIN, M.G., ZURLE, M.G., MACCHIA, P., MANCINI, A., INDOLFI, P., LOCURTO, M., CALCULLI, G., CRISTIANI, M. & CASTELLO, M. (1988). Etoposide in recurrent childhood Langerhans cell histiocytosis: an Italian cooperative study. *Cancer*, **62**, 2528-2551.
- CECI, A., DE TERLIZZI, M., TOMA, M.G., CALCULLI, G., CAPUTO, R.J., CASTELLO, M., INDOLFI, P. & ROSATI, D. (1988). Heterogeneity of immunological patterns in Langerhans Histiocytosis and response to crude calf thymic extract in 11 patients. *Med. Ped. Oncol.*, **16**, 111-115.
- CECI, A., DE TERLIZZI, M., COLELLA, R., LOIACONO, G., BALUCCI, D., SARICO, G., CASTELLO, M., TESTI, A.M., DE BERNADI, B., INDOLFI, P., MACCHIA, P., MADON, E., MANCINI, A. & ROSATI, D. (1993). Langerhans Cell Histiocytosis in Childhood: Results from the Italian Cooperative AIEOP-CNR-H.X'83 Study. *Med. Pediatr. Oncol.*, **21**, 259-264.
- DANESHBOOD, K. & KISSANE, J.M. (1978) Idiopathic differentiated histiocytosis. *Amer. J. of Clin. Pathol.*, **70**, 381-386.
- DAVIES, E.G., LEVINSKY, R.J., BUTLER, M., BROADBENT, V., PRITCHARD, J. & CHESSELLS, J. (1983). Thymic hormone therapy for histiocytosis X? *N. Engl. J. Med.*, **309**, 493-494.
- ECKSTEIN, R., HUHNS, D., SCHNEIDER, B., HEIM, M.U., PELTZ, F., MULLER, R., EDLMANN, M., LOHR, G. & MEMPEL, W. (1985). Beeinflussung immunfunktioneller Parameter bei Histiocytose-X durch Thymostimulin. *Arznei. Forsch/Drug Res.*, **35**, 155-162.
- EGELER, R.M., THOMPSON, R.C., VOUTE, P.A. & NESBIT, M.E. Intralésional infiltration of corticosteroids in localized Langerhans cell histiocytosis. *J. Pediatr. Orthop.*, **12**, 811-814.
- EGELER, R.M., DE KRAKER, J. & VOUTE, P.A. (1993). Cytosine-araboside, vincristine, and prednisolone in the treatment of children with disseminated Langerhans cell histiocytosis with organ dysfunction: experience at a single institution. *Med. Ped. Oncol.*, **21**, 265-270.
- FELDGES, A. (1981). Childhood histiocytosis X: clinical aspects and therapeutic approaches. *Haematol. and Blood Transfusion*, **27**, 225-229.
- GADNER, H., HEITGER, A., GROIS, N., GATTERER-MENZ, I. & LADISCH, S. (1994). A treatment strategy for disseminated Langerhans cell histiocytosis. *Med. Ped. Oncol.*, **23**, 72-80.
- GRAMATOVICI, R. & D'ANGIO, G.J. (1988). Radiation therapy in soft-tissue lesions in Histiocytosis X (Langerhans' Cell Histiocytosis). *Med. Ped. Oncol.*, **16**, 259-262.
- GREENBERGER, J.S., CROCKER, A.C., VAWTER, G., JAFFE, N. & CASSADY, J.R. (1981). Results of treatment of 127 patients with systemic histiocytosis (Letterer-Siwe Syndrome, Schuller-Christian Syndrome and multifocal eosinophilic granuloma). *Medicine*, **60**, 311-338.
- GREINIX, H.T., STORB, R., SANDERS, J.E. & PETERSEN, F.B. (1992). Marrow transplantation for treatment of multisystem progressive Langerhans cell histiocytosis. *Bone Marrow Transplantation*, **10**, 39-44.
- GROIS, N., FLUCHER-WOLFRAM, B., HEITGER, A., GATTERER-MENZ, J., MOSTBECK, G.H. & GADNER, H. Diabetes insipidus in Langerhans cell histiocytosis. *Med. Ped. Oncol.*, (in press).
- HALTON, J., WHITTON, A., WIERNIKOWSKI, J. & BARR, R.D. (1992). Disseminated Langerhans cell histiocytosis in identical twins unresponsive to recombinant human  $\alpha$ -interferon and total body irradiation. *Am. J. Ped. Hematol. Oncol.*, **14**, 269-272.
- HAWKINS, M.M., WILSON, L.M., STOVALL, M.A., MARSDEN, H.B., POTOK, M.H.N., KINGSTON, J.E. & CHESSELLS, J.M. (1992). Etoposide, given with alkylating agents, and radiation associated with an increased risk of secondary leukaemia after childhood cancer. *Brit. Med. J.*, **304**, 951-958.
- HISTIOCYTE SOCIETY WRITING GROUP (1987). Histiocytosis syndromes in children. *Lancet*, **i** 208-209.
- JAKOBSON, M., KREUGER, A., HAGBERG, H. & SUNDSTROM, C. (1987) Treatment of Langerhans cell histiocytosis with alpha-interferon. *Lancet*, **2**, 1520.
- KOMP, D.M., VIETTI, T.J., BERRY, D.H., STARLING, K.A., HAGGARD, M.E. & GEORGE, S.L. Combination chemotherapy in histiocytosis X. *Med. Ped. Oncol.*, **3**, 267-273.
- KOMP, D.M., EL MAHDI, A., STARLING, K.A., EASLEY, J., VIETTI, T.J., BERRY, D.H. & GEORGE, S.L. (1980). Quality of survival in histiocytosis X: a Southwest Oncology Group Study. *Med. Ped. Oncol.*, **8**, 35-40.
- KOMP, D.M. (1981). Long-term sequelae of Histiocytosis X. *Am. J. Pediatr. Hematol. Oncol.*, **3**, 165-168.
- LADISCH, S. (1983) Histiocytosis. In: Willoughby MLN, Siegel SE, ed. *Butterworth's International Medical Reviews, Hematology and Oncology, Pediatrics 1*. Butterworth Scientific, 95-109.
- LADISCH, S., GADNER, H., ARICO, M., BROADBENT, V., GROIS, N., JAKOBSON, A., KOMP, D. & NICHOLSON, H. (1994) LCH-I: A randomized trial of etoposide versus vinblastine in disseminated Langerhans cell histiocytosis. *Med. Ped. Oncol.*, **23**, 107-110.
- LAHEY, M.E. (1962). Prognosis in reticuloendotheliosis in children. *J. Pediatr.*, **60**, 664-668.
- LAHEY, M.E. (1975). Histiocytosis X: an analysis of prognostic factors. *J. Pediatr.*, **87**, 184-189.
- LAHEY, M.E., SMITH, B. & HEYN, R. (1979). Immunologic studies in histiocytosis X. *Proc. Am. Assoc. Cancer. Res.*, **20**, 436.
- MAHMOUD, H.H., WANG, W.C. & MURPHY, S.B. (1991). Cyclosporine therapy for advanced Langerhans cell histiocytosis. *Blood*, **77**, 721-725.
- MAHMOUD, H. & BROADBENT, V. (1993). Results of the Histiocyte Society cyclosporine salvage therapy questionnaire. Proc. Ninth Annual Meeting Histiocyte Society.
- MATHUS-RIDLEY, M., RANEY, R.B., THAWERUI, H. & MEADOWS, A.T. (1983). Histiocytosis X in children: patterns of disease and results of treatment. *Med. Ped. Oncol.*, **11**, 99-105.
- MCLELLAND, J., BROADBENT, V., YEOMANS, E., MALONE, M. & PRITCHARD, J. (1990). Langerhans cell histiocytosis: the case for conservative treatment. *Arch. Dis. Child.*, **65**, 301-303.
- NEUMANN, C., KOLDE, G. & BONSMANN, G. (1988) Histiocytosis X in an elderly patient. Ultrastructure and immunohistochemistry after PUVA photochemotherapy. *Br. J. Dermat.*, **119**, 385-391.

- NEZELOF, C., FRILEUX-HERBET, F. & CRONIER-SACHOT, J. (1979) Disseminated histiocytosis X. Analysis of prognostic factors based on a retrospective study of 50 cases. *Cancer*, **44**, 1824-1838.
- OBERMAN, H.A. (1961) Idiopathic histiocytosis. A clinicopathologic study of 40 cases and review of the literature. *Pediatrics*, **28**, 307-327.
- OSBAND, M.E., LIPTON, J.M., LAVIN, P., LEVEY, R., VAWTER, G., GREENBERGER, J.S., MCCAFFREY, R.P. & PARKMAN, R. (1981) Histiocytosis X: Demonstration of abnormal immunity, T-cell histamine H2-receptor deficiency and successful treatment with thymic extract. *New Engl. J. Med.*, **304**, 146-153.
- RANEY, R.B. & D'ANGIO, G.J. (1989) Langerhans cell histiocytosis (histiocytosis X): Experience at the Children's Hospital of Philadelphia, 1970-1984. *Med. Ped. Oncol.*, **17**, 20-28.
- RINGDEN, O., AHSTROM, L., LONQVIST, B., BARYD, I., SVEDMYR, E. & GAHRTON, N.G. (1987) Allogenic bone marrow transplantation in a patient with chemotherapy-resistant progressive histiocytosis X. *N. Engl. J. Med.*, **316**, 733-735.
- SELCH, M.T. & PARKER, R.G. (1990) Radiation therapy in the management of Langerhans cell histiocytosis. *Med. Ped. Oncol.*, **18**, 97-102.
- SHEEHAN, M.P., ATHERTON, D.J., BROADBENT, V. & PRITCHARD, J. (1991) Topical nitrogen mustard: An effective treatment for cutaneous Langerhans cell histiocytosis. *J. Pediatr.*, **119**, 317-321.
- STOLL, M., FREUND, M., SCHMID, H., DEICHER, H., REIHM, H., POLIWODA, H. & LINK, H. (1990) Allogenic bone marrow transplantation for Langerhans cell histiocytosis. *Cancer*, **66**, 284-288.
- TOOGOOD, I.R.G., ELLIS, W.M. & EKERT, H. (1979) Prognostic criteria, treatment and survival in disseminated histiocytosis X. *Aus. Paediatr.*, **15**, 91-95.
- VIANA, M.B., OLIVEIRA, B.M., SILVA, C.M. & LEITE, V.H.R. (1991) Etoposide in the treatment of six children with Langerhans cell histiocytosis (Histiocytosis X). *Med. Ped. Oncol.*, **19**, 289-294.