ELSEVIER

European Journal of Cancer 41 (2005) 2592–2594

European Journal of Cancer

www.ejconline.com

Editorial Comment

Getting there? Salvage therapy for refractory Langerhans cell histiocytosis in children

Sheila Weitzman MB [a,*], Jon Pritchard FRCPCH [b]

[a] *Department of Haematology/Oncology, Hospital for Sick Children, 555 University Avenue, Toronto, Ont, Canada*
[b] *Department of Haematology/Oncology, Royal Hospital for Sick Children, Edinburgh, UK*

Received 1 July 2005; accepted 5 July 2005
Available online 16 September 2005

Multisystem Langerhans Cell Histiocytosis (MS-LCH) is seen in both adults and children and its natural history varies from a chronic grumbling disease, often leaving permanent sequelae to a rapidly progressive treatment-resistant form. Deaths are usually in infants, in the severe form of LCH once known as 'Letterer-Siwe disease.' In successive paediatric cooperative trials, starting with the early German–Austrian DAL HX-83 and DAL HX-90, through the trials of the International Histiocyte Society LCH-I and LCH-II, all with conscientiously collected data and quality control, the mortality for this group of patients has remained between 15% and 20% [1,2]. In these trials, involvement of so called 'risk organs' (lungs, liver, spleen, and haematopoietic system) predicts a 'high risk' group of patients – 10–20% of the total-with life threatening disease. It became apparent from these studies, and from a review by the French Histiocytosis study group encompassing 348 patients [3], that the response to 'standard' induction therapy with corticosteroids and vinblastine usually judged at 6 weeks from diagnosis, was the single most important prognostic factor. The probability of survival for patients in the LCH-I and II studies who failed to respond after 2 cycles of this therapy, – *i.e.*, at 6 weeks from diagnosis – was only 20–34% [2,4] and was as low as 10% after more 'intensive' DAL induction therapy [1].

It became apparent fairly early, therefore, that children with MS-LCH who failed to respond to therapy should move quickly to a 'salvage protocol', if mortality was to be reduced. The problem has been that, despite a great deal of effort by many clinicians, it has been difficult to identify treatment that is active in patients with LCH that is refractory to 'standard induction therapy', which now may also include methotrexate (LCH-III experimental arm). In this issue of the *European Journal of Cancer*, Dr. Bernard and his colleagues describe and discuss the important findings of their pilot study of combined 2-chlorodeoxyadenosine (2-CdA) and cytosine arabinoside (ara-C) in French children with 'haematopoetic dysfunction'.[1] Successful therapy with single agent etoposide [5], cyclosporine-A [6] and combinations such as vincristine, ara-C and corticosteroid have been described in case reports and small institution-based series [7] but when tested in larger studies none of these approaches has proven to be consistently successful in 'refractory' patients [8].

So, how was the ara-C/2-CdA combination derived? Since the report by Saven and colleagues [9], many case reports and some small series have demonstrated activity of 2-CdA in LCH, first in adults then in children [10–12]. The results of the recently closed Histicyte Society LCH-S-98 trial of 2-CdA monotherapy as 'salvage' treatment in LCH showed that around one third of 'high risk' patients responded. As with cyclosporin A [13] the results were better in chronically reactivating 'low risk' LCH [14]. The multiple effects of 2-CdA on DNA

[1] Haematopoetic failure is usually defined as pancytopenia or bicytopenia. Commonly known as 'bone marrow failure', the reduction in blood counts is almost certainly due to a secondary macrophage activation syndrome, provoked by the underlying LCH, rather than by actually bone marrow infiltration. The old description ('bone marrow failure') is therefore probably inappropriate [8].

* Corresponding author. Tel.: +1 416 813 8886; fax: +1 416 813 5327.
E-mail address: sheila.weitzman@sickkids.ca (S. Weitzman).

0959-8049/$ - see front matter
doi:10.1016/j.ejca.2005.07.008

metabolism, however, means that it is likely to be at least additive and possibly synergistic with many cytotoxic drugs including ara-C [15].

Ara-C was 'first choice' because the combination of 2-CdA and ara-C results in higher intracellular concentrations and/or increased retention time of the cytotoxic ara-C metabolite 5-triphosphate-araCTP both *in vitro* and *in vivo* in acute myelobastic leukaemia [16,17]. Since 'LCH cells' – the 'tumour cells' in LCH – are ontogenetically related to the myeloid series, it seems reasonable to assume that there may also be synergy against LCH. In addition, their efficacy individually in LCH, their reported ability to cross the blood–brain barrier [18] and their efficacy in 'active' CNS LCH [19,20] are all attractive characteristics of this combination. No one knows as yet, the unwanted 'late effects' of 2-CdA in children but ara-C probably has low long term toxicity, which is an especially appealing feature when most patients are young children.

What other salvage strategies are currently being investigated in LCH? Anti-CD1a monoclonal antibodies are possible reagents or vectors for 'targeted' therapy but so far, no acceptably non-toxic reagent has been developed [21]. Others have used marrow-ablative therapy, followed by stem-cell transplantation (SCT) in patients with refractory LCH on the basis that it is a leukaemia-like condition which will not be cured unless the patient's bone marrow is destroyed in its entirety, then replaced with a healthy bone marrow graft. Allogeneic stem-cell transplantation in LCH is theoretically attractive because immune deregulation is thought to be an integral part of the pathogenesis of the disease. Three potential mechanisms may contribute in the successful control of refractory LCH by marrow-ablative therapy followed by an allogeneic graft, namely, the cytotoxic effect of high dose chemotherapy, a graft-*versus*-LCH effect and replacement of the recipient's immune system by that of the donor.

In this regard, it has been demonstrated that, following successfully allogeneic transplantation, recipient normal Langerhans cells are gradually replaced by donor Langerhans cells [22]. A recent review identified 27 cases of stem-cell transplantation [23]. Fourteen of the 27 (52%) patients were alive in continuous complete remission from 12+ to 144+ (median 25+) months, 13 after allogeneic stem-cell transplantation and one after autologous transplantation. As with patients with leukaemia treated in a similar manner, most of the autologous stem-cell recipients relapsed, whereas most deaths after allogenic transplantation were due to toxicity, raising the possibility that reduced-intensity allogeneic transplants ('mini-transplants') may be a useful alternative. Unfortunately, but not surprisingly, positive reporting bias is a major obstacle to drawing definite conclusions about 'experimental' approaches such as these. The Histiocyte Society is therefore planning a prospective trial of marrow-ablative therapy and stem-cell transplantation in LCH patients refractory to other approaches.

Better 'standard dose' chemotherapy is also needed for two reasons. First, if patients respond better to less intensive induction regimens, marrow-ablative therapy may not be necessary at all and, second, even if a bone marrow transplant is carried out, the medical condition – as regards their nutrition, infection status and risk of bleeding – of patients being 'worked up' for that treatment need to be improved to try to reduce the high morbidity of the subsequent high dose/transplant procedure. Pilot studies such as the one reported in this issue are, therefore, of great importance. Dr. Bernard and his colleagues, all members of the French Histiocyte Society study group, evaluated the 2-CdA/ara-C combinations in 10 patients, all but one of whom had failed multiple previous therapies ('refractory LCH'). Seven of the 10 patients received at least 2 courses of 2-CdA/ara-C, 2 others died soon after the first course and one was changed to alternative therapy, including stem cell transplant. The toxicity of the 2 drug regimen is difficult to evaluate since almost all the patients already had 'haematopoietic failure' (pancytopenia) due to LCH. Many were therefore infected, anaemic and thrombocytopenic before they started 2-CdA/ara-C. Nevertheless, all the patients suffered severe myelosuppression and 2 died from infectious complications. The investigators used a newly devised scoring system to evaluate disease activity at diagnosis and response to therapy [24]. Whilst promising, this system has not been validated by other groups and the French study would have been enhanced if traditional LCH response criteria had also been used alongside their new system. Another problem is that all but one of the patients received additional therapy prior to achieving 'no active disease (NAD)' status resulting in an element of uncertainty as to whether any or all of the responses were due solely to the 2 drug combinations. The results of Dr. Bernard and colleagues study do need to be verified and it would be better if the important issue – ''Is 2-CdA/ara-C a real breakthrough?' was verified by a larger, 'cleaner' study. Interpretation of the French data is also difficult because of the small number of patients but the investigators are to be congratulated on successfully entering 9 of the 12 'refractory LCH' patients identified by the French Oncology Centres during the 3 year study period. Very few national Study Groups can manage this degree of 'compliance', especially in a pilot study. A further problem is that the patients appear to belong to two possibly different subgroups. Five of the 10 patients had responded to their initial therapy but were later refractory to the same therapy; it is noteworthy that all 3 patients who were not evaluable for response, because of early death or removal from the study, were in the second group of 5 patients with 'poor' initial response, suggest-

ing that the results may not be as good on this second group of patients. Despite these caveats, the response rate of 70% achieved in Dr. Bernard and colleagues' study and the fact that all responders achieved disease free status and remained alive at a median follow-up time of 36+ months really is encouraging. This result is better than that obtained in the Histiocyte Society's 2-CdA monotherapy study in which most of the non-responders developed progressive disease and died [14]. Certainly the French results are sufficiently promising to lay the foundation for a new Histiocyte Society salvage protocol, which is now being planned and should be open to international accrual within the next 12 months.

Are we 'getting there'? It is hard to be sure from this relatively small pilot study but we regard this result as, at the very least, being intriguing and, at the best, the most encouraging 'relapse' study ever carried out in children with Langerhans Cell Histiocytosis.

Conflict of interest statement

None declared.

References

1. Minkov M, Grois N, Heitger A, *et al*. Response to initial treatment of multisystem Langerhans cell histiocytosis: an important prognostic indicator. *Med Pediatr Oncol* 2002, **39**, 581–585.
2. Gadner H, Grois N, Arico M, *et al*. A randomized trial of treatment for multisystem Langerhans' cell histiocytosis. *J Pediatr* 2001, **138**, 728–734.
3. The French LCH Study Group. A multicentre retrospective survey of LCH: 348 cases observed between 1983 and 1993. *Arch Dis Child* 1996, **75**, 17–24.
4. Ladisch S, Gadner H, Aricó M, *et al*. A randomized trial of etoposide *vs.* vinblastine in disseminated Langerhans cell histiocytosis. *Med Pediatr Oncol* 1994, **23**, 107–110.
5. Ceci A, de Terlizzi M, Colella R, *et al*. Etoposide in recurrent childhood Langerhans' cell histiocytosis: an Italian cooperative study. *Cancer* 1988, **62**, 2528–2531.
6. Mahmoud H, Wang W, Murphy S. Cyclosporine therapy for advanced Langerhans cell histiocytosis. *Blood* 1991, **77**, 721–725.
7. Egeler RM, de Kraker J, Voûte PA. Cytosine-arabinoside, vincristine, and prednisolone in the treatment of children with disseminated Langerhans cell histiocytosis with organ dysfunction: experience at a single institution. *Med Pediatr Oncol* 1993, **21**, 265–270.
8. Arceci RJ, Brenner MK, Pritchard J. Controversies and new approaches to treatment of Langerhans cell histiocytosis. *Haematol Oncol Clin N Am* 1998, **12**, 339–357.
9. Saven A, Foon K, Piro L. 2-Chlorodeoxyadenosine induced complete remissions in Langerhans cell histiocytosis. *Ann Intern Med* 1994, **21**, 430–432.
10. Saven A, Burian C. Cladribine activity in adult Langerhans cell histiocytosis. *Blood* 1999, **93**, 4125–4130.
11. Stine KC, Saylors RL, Willimas LL, *et al*. 2-Chorodeoxyadenosine(2-CdA) for the treatment of refractory or recurrent Langerhans cell histiocytosis (LCH) in pediatric patients. *Med Pediatr Oncol* 1997, **29**, 288–292.
12. Rodriguez-Galindo C, Kelly P, Jeng M, *et al*. Treatment of children with Langerhans cell histiocytosis with 2-chlorodeoxyadenosine. *Am J Hematol* 2002, **69**, 179–184.
13. Minkov M, Grois N, Broadbent V, *et al*. Cyclosporine A therapy for multisystem Langerhans cell histiocytosis. *Med Pediatr Oncol* 1999, **33**, 482–485.
14. Weitzman S, Arceci R, Braier J, *et al*. 2-Chlorodeoxyadenosine (2-CDA) as salvage therapy for Langerhans cell histiocytosis (LCH). Results of LCH-S-98. *Pediatr Blood Cancer* 2005, **45**, 95.
15. Choi SW, Bangaru BS, Wu CD, *et al*. Gastrointestinal involvement in disseminated Langerhans cell histiocytosis (LCH) with durable complete response to 2-chlorodeoxyadenosine and high-dose cytarabine. *J Pediatr Hematol Oncol* 2003, **25**, 503–506.
16. Gandhi V, Estey E, Keating MJ, *et al*. Chlorodeoxyadenosine and arabinosylcytosine in patients with acute myelogenous leukemia: pharmacokinetic, pharmacodynamic and molecular interactions. *Blood* 1996, **87**, 256–264.
17. Crews KR, Gandhi V, Srivastava DK, *et al*. Interim comparison of a continuous infusion *versus* a short daily infusion of cytarabine given in combination with cladribine for pediatric acute myeloid leukemia. *J Clin Oncol* 2002, **20**, 4217–4224.
18. Liliemark J, Juliusson G. On the pharmacokinetics of 2-chloro-2-deoxyadenosine (CdA) in cerebrospinal fluid(CSF). *Blood* 1992, **80**.
19. Watts J, Files B. Langerhans cell histiocytosis: central nervous system involvement treated successfully with 2-chlorodeoxyadenosine. *Pediatr Hematol Oncol* 2001, **18**, 199–204.
20. Ottaviano F, Finlay JL. Diabetes Insipidus and Langerhans cell histiocytosis: a case report of reversibility with 2-chlorodeoxyadenosine. *J Pediatr Hematol/Oncol* 2003, **25**, 575–577.
21. Kelly KM, Pritchard J. Monoclonal antibody therapy in Langerhans cell histiocytosis-feasible and reasonable? *Br J Cancer* 1994, **23**(Suppl.), S54–S55.
22. Perreault C, Pelletier M, Landry D, *et al*. Study of Langerhans cells after allogeneic bone marrow transplantation. *Blood* 1984, **63**, 807–811.
23. Weitzman S, McClain K, Arceci R. Treatment of relapsed and/or refractory Langerhans cell histiocytosis. In Weitzman S, Egeler RM, eds. *Histiocytic Disorders of Children and Adults*. Cambridge, Cambridge University Press, 2005. pp. 254–271.
24. Donadieu J, Piguet F, Bernard M, *et al*. A new clinical score for disease activity in Langerhans cell histiocytosis. *Pediatr Blood Cancer* 2004, **43**, 770–776.