Treatment of adult-onset Langerhans cell histiocytosis—is it different from the pediatric approach?

In this issue of *Annals of Oncology* E. Derenzini et al. [1] report on results of a single-center study in treating adult patients with Langerhans cell histiocytosis (LCH) with the third-generation chemotherapy regimen 'MACOP-B', conceived and employed for aggressive non-Hodgkin lymphomas (NHL). This course of intensive therapy consisting of prednisone, vincristine, bleomycin, methotrexate, doxorubicin, and cyclophosphamide was given to seven patients suffering from extended LCH from 1995 to 2007. Three patients presented with multisystem Langerhans cell histiocytosis (MS-LCH), including lung and liver involvement, and four patients with single-system multifocal bone (SS-MFB) disease. The 'MACOP-B' course was repeated for 12 weeks and no continuation therapy was given. Response evaluation by computed tomography (CT) and magnetic resonance imaging (MRI) was done after 6 and 12 weeks in all patients, and positron emission tomography (PET) was additionally used in four consecutive patients since 2004. Response was achieved in all patients (two partial responses, five complete responses) and three recurrences were seen after stopping therapy. Two of them died due to disease progression. Negative PET scan was consistent with recurrence-free survival, except in one patient who recurred 5 years later. In conclusion, the authors emphasize the effectiveness of an aggressive NHL protocol in getting rapid response in MS-LCH and SS-MFB-LCH and highlight the usefulness of PET scan for detection of active disease at diagnosis, response evaluation, and assessment in case of recurrence.

The results of this study have to be interpreted with caution due to the small number of patients, the retrospective character of the analysis, and the relatively long period of data collection. Nevertheless, it clearly reflects the lack of evidence and illustrates the need for accorded strategy in the treatment of adult-onset LCH. In the process of search for optimal management of adult LCH, it may be helpful to consider common aspects with pediatric LCH and the respective knowledge gained in controlled clinical trials.

Chemotherapeutic regimens derived from leukemia and lymphoma trials have been applied in LCH patients from the 1960s to the 1980s, as at that time the disease was thought to be a malignancy. About 25 years ago, experts of the Histiocyte Society decided to avoid the use of alkylating agents and anthracyclines in pediatric LCH at all or at least in the front-line therapy. This was partly driven by the belief that LCH is a reactive rather than malignant process and partly by concerns for therapy-related late effects. Nowadays, very intensive therapy is reserved for salvage of severely ill patients, who do not respond to standard treatment [2–4].

LCH is a disease with extremely variable clinical presentation and unpredictable course in both children and adults. The need for risk-adapted therapy has been revealed in a number of retrospective and prospective pediatric trials. It has been unequivocally proven that patients with single-system Langerhans cell histiocytosis (SS-LCH) of the skeleton (including patients with MFB disease) have excellent survival chances and challenges remaining are acute morbidity, risk for disease reactivation, and disease-related permanent consequences [5–7]. In contrast to malignant diseases, LCH lesions and, in particular, osseous lesions can spontaneously heal. Hence, treatment intensity and potential toxicity have to be adjusted accordingly. On the other hand, patients with MS-LCH may have a more unpredictable course, including rapid deterioration with fatal outcome. Some studies from the early 1980s have shown the merit of systemic risk-adjusted combination therapy commenced promptly after diagnosis, in improving survival and reducing reactivation rates in MS-LCH [8–10].

These studies formed the basis for the international prospective randomized trials (LCH-I, LCH-II, and LCH-III), conducted by the Histiocyte Society since the early 1990s, after worldwide acceptance of uniform diagnostic criteria and disease stratification (SS-LCH versus MS-LCH with/without risk-organ involvement).

The results of these studies demonstrate that a high proportion of patients with MS-LCH do not deserve toxic therapy and that most of them can be cured with a common standard therapy consisting of steroids and vinblastine [11, 12]. Whether this combination will be equally effective and well tolerated in adults is a matter of an ongoing international trial of the Histiocyte Society (LCH-A1).

Involvement of the so-called ‘risk organs’ (liver, spleen, hematopoietic system, and lungs) at the time of diagnosis is a well-established unfavorable prognosticator in children with MS-LCH [11, 13–15]. Apart from risk-organ involvement, response to initial therapy was found to be another reliable prognostic predictor in pediatric MS-LCH [11, 16]. Patients with rapid response within 6 weeks have a survival probability of up to 90% and those who do not respond adequately only 40%. It has been shown that mortality is largely restricted to patients with risk-organ involvement at diagnosis and especially to those who do not responding adequately to initial therapy. These prognostic parameters allow for patient stratification and therapy adjustment in pediatric patients and still remain to be prospectively studied in adults with MS-LCH. Appropriate
stratification in adult LCH may allow reducing treatment intensity in the majority of patients and reserving the regimen used by E. Derenzini et al. for patients with poor prognosis.

In both SS-LCH and MS-LCH pediatric patients, the continuation therapy seems to play an important role for a permanent disease control and prevention of recurrences (unpublished data of the Histiocyte Society LCH Study Group, Chair H Gadner). Although the optimal length is still to be defined, this aspect has to be considered also in adult patients.

The pediatric trials could not reliably address the prognostic significance of pulmonary involvement with the context of an MS-LCH as in children it is usually combined with other risk organs. Nevertheless, it seems that lung involvement in the absence of involvement of other risk organs does not confer unfavorable prognosis [17] and does not justify aggressive therapy.

While response can be reliably measured in most organs, defining disease activity of bone lesions by the means of X-ray, CT or MRI is quite challenging. Application of PET scan for evaluation of disease activity in LCH seems quite promising [18, 19]. However, to date, there is only limited experience on the basis of small series and a prospective large-scale validation is needed before its routine use for therapeutic decisions.

In summary, despite a few critical comments, the report by E. Derenzini et al. [1] represents an essential initiative for sharing knowledge regarding management of extended LCH in adults. It reveals the lack of uniform management approach for adults with disseminated LCH and underscores the need for risk-adapted systemic therapy. With this respect, ‘MACOP-B’ regimen could be prospectively studied as a salvage therapy in adult patients with resistant or progressive MS-LCH: may be as an international trial under the umbrella of the Histiocyte Society?

H. Gadner*
Department of Hemato/Oncology,
St Anna Children’s Hospital,
Vienna, Austria
(*E-mail: h.gadner@stanna.at)

references