

- characterize a new subset of chronic lymphocytic leukemia. *Blood* 2002; 99:2262-4.
7. Oscier DG, Thompssett A, Zhu D, Stevenson FK. Differential rates of somatic hypermutation in VH genes among subsets of chronic lymphocytic leukemia defined by chromosomal abnormalities. *Blood* 1997; 89:4153-60.
 8. Oscier DG, Gardiner AC, Mould SJ, Glide S, Davies ZA, Ibbotson RE, et al. Multivariate analysis of prognostic factors in CLL: clinical stage, IGVH gene mutational status, and loss or mutation of the p53 gene are independent prognostic factors. *Blood* 2002; 100:1177-84.
 9. Krober A, Sella T, Benner A, Bullinger L, Brucke E, Lichter P, et al. VH mutation status, CD38 expression level, genomic aberrations, and survival in chronic lymphocytic leukemia. *Blood* 2002; 100:1410-6.
 10. Lin K, Sherrington P, Dennis M, Matrai Z, Cawley JC, Pettitt AR. Relationship between p53 dysfunction, CD38 expression, and IgVH mutation in chronic lymphocytic leukemia. *Blood* 2002; 100:1404-9.
 11. Nollet F, Cauwelier B, Billiet J, Sellesiaq D, Van Hoof A, Louwagie A, et al. Do B-cell chronic lymphocytic leukemia patients with IgVH 3-21 genes constitute a new subset of chronic lymphocytic leukemia? *Blood* 2002; 100:1097-8.
 12. Damle RN, Ghiotto F, Valetto A, Albesiano E, Fais F, Yan XJ, et al. B-cell chronic lymphocytic leukemia cells express a surface membrane phenotype of activated, antigen-experienced B lymphocytes. *Blood* 2002; 99:4087-93.
 13. Klein U, Rajewsky K, Kuppers R. Human immunoglobulin (Ig)M⁺ IgD⁺ peripheral blood B cells expressing the CD27 cell surface antigen carry somatically mutated variable region genes: CD27 as a general marker for somatically mutated (memory) B cells. *J Exp Med* 1998; 188:1679-89.
 14. Rosenwald A, Alizadeh AA, Widhopf G, Simon R, Davis RE, Yu X, et al. Relation of gene expression phenotype to immunoglobulin mutation genotype in B cell chronic lymphocytic leukemia. *J Exp Med* 2001; 194:1639-47.
 15. Klein U, Tu Y, Stolovitzky GA, Mattioli M, Cattoretti G, Husson H, et al. Gene expression profiling of B cell chronic lymphocytic leukemia reveals a homogeneous phenotype related to memory B cells. *J Exp Med* 2001; 194:1625-38.
 16. Orchard JA, Ibbotson RE, Davis ZA, Gardiner AC, Hamblin TJ, Oscier DG. Zap-70 evaluation by flow cytometry is a significant prognostic marker in B-CLL. *Blood* 2002; 100 Suppl 1:[abstract](in press).
 17. Caligaris-Cappio F, Hamblin TJ. B-cell chronic lymphocytic leukemia: a bird of a different feather. *J Clin Oncol* 1999; 17:399-408.
 18. Stankovic T, Stewart GS, Fegan C, Biggs P, Last J, Byrd PJ, et al. Ataxia telangiectasia mutated-deficient B-cell chronic lymphocytic leukemia occurs in pregerminal center cells and results in defective damage response and unrepaired chromosome damage. *Blood* 2002; 99:300-9.
 19. McCarthy H, Wierda WG, Barron LL, Cromwell C, Keating MJ, Abruzzo LV. CLL patients with unmutated immunoglobulin VH genes express high levels of activation-induced cytidine deaminase (AID) mRNA and splice variants. *Blood* 2002; 100 Suppl 1:[abstract](in press).
 20. Albesiano E, Messmer BT, Damle RN, Allen SL, Kudalkar PR, Koilitz JE, et al. Activation-induced cytidine deaminase (AID) expression in B-CLL. *Blood* 2002; 100 Suppl 1:[abstract](in press).
 21. Oppezio P, Vuillier F, Vasconcelos Y, Magna C, Dumas G, Payelle-Brogard B, et al. CLL-B-cells expressing AID display a dissociation between class switch recombination and somatic hypermutation. *Blood* 2002; 100 Suppl 1:[abstract](in press).
 22. Anonymous. Chemotherapeutic options in chronic lymphocytic leukemia: a meta-analysis of the randomized trials. CLL Trialists' Collaborative Group. *J Natl Cancer Inst* 1999; 91:861-8.

Management of primary mediastinal B-cell lymphoma with sclerosis: advances and caveats

Primary mediastinal B-cell lymphoma with sclerosis is a distinctive subtype of non-Hodgkin's lymphoma with unique clinicopathologic aspects and aggressive behavior.¹ In 1997 Lazzarino *et al.*² reported studies on 106 patients, 99 of whom received doxorubicin-containing chemotherapy. Thirty-five of 99 patients were primarily chemotherapy-resistant, and 64 responded: most of the responders received mediastinal radiotherapy. The actuarial 3-year survival rate was 52% for all patients and 82% for responders. Poor performance status and pericardial effusion predicted non response and poor survival. Inadequate response after the first courses of front-line chemotherapy predicted failure of subsequent treatment. Responders with a bulky mediastinum or residual mediastinal abnormality after chemotherapy were at risk of relapse. Retrospective studies are useful in trying to define the natural history of rare disorders, and this may apply to primary mediastinal B-cell lymphoma with sclerosis, which represents about 3% of non-Hodgkin's lymphomas. However, retrospective studies have major drawbacks, and one limitation in this case might be the appropriateness of the histologic diagnosis.³ It cannot be excluded that retrospective studies include cases of diffuse large cell lymphoma that have a more favorable prognosis.

There is no question that primary mediastinal B-cell lymphoma with sclerosis requires aggressive treatment. In a report in this journal on 89 patients, Zinzani *et al.*⁴ showed that combined modality treatment using the MACOP-B chemotherapy regimen and radiation therapy induced a good remission rate with the patients having a greater than 90% chance of surviving disease-free at 9 years. They also emphasized that radiotherapy often plays a pivotal role in obtaining complete remission status. In this issue, Zinzani *et al.*⁵ report observations on 426 patients diagnosed with primary mediastinal B-cell lymphoma with sclerosis in 20 institutions from different countries. This retrospective study strongly suggests that MACOP-B (or similar third-generation chemotherapy regimens such as VACOP-B) plus radiation therapy represents the best therapeutic option for most of these patients, with the long-term overall survival being as high as 70-75%. On the other hand, patients with predic-

tive factors of poor outcome are likely candidates for high-dose sequential chemotherapy plus autologous stem cell transplantation (ASCT).

However, there is no consensus at present on predictive factors of poor outcome in patients with primary mediastinal B-cell lymphoma with sclerosis. Previous studies have singled out less than partial midway response to chemotherapy, pericardial effusion, bulky disease and IPI score ≥ 2 .¹⁻³ Cairoli *et al.*⁶ have recently evaluated the impact of an early intensification program including chemotherapy, ASCT and radiation therapy (RT) in patients presenting with adverse prognostic factors (high-intermediate or high risk group according to the age-adjusted International Prognostic Index. Induction therapy consisted of VACOP-B (etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin) for 12 weeks. Of 15 poor risk patients, five achieved complete remission, seven partial remission, and three showed refractory disease. All these patients received mobilizing therapy consisting of high-dose cyclophosphamide. After transplantation using BEAM as the preparative regimen, all patients but one achieved a complete remission. At a median follow-up of 35 months from transplantation the disease-free survival was 93%. This program of early intensification appears an interesting approach to treatment of poor risk patients. Because of the current uncertainties the time has come for a prospective multicenter trial aimed at defining a risk-adapted approach to treatment of primary mediastinal B-cell lymphoma with sclerosis.

Mario Lazzarino, Ester Orlandi
Division of Hematology
University of Pavia & IRCCS Policlinico S. Matteo
27100 Pavia, Italy
E-mail: mlazzarino@smatteo.pv.it

References

1. Lazzarino M, Orlandi E, Paulli M, Boveri E, Morra E, Brusamolino E, et al. Primary mediastinal B-cell lymphoma with sclerosis: an aggressive tumor with distinctive clinical and pathologic features. *J Clin Oncol* 1993; 11:2306-13.
2. Lazzarino M, Orlandi E, Paulli M, Strater J, Klersy C, Gianelli U, et al. Treatment outcome and prognostic factors for primary mediastinal (thymic) B-cell lymphoma: a multicenter study of 106 patients. *J Clin Oncol* 1997; 15:1646-53.
3. Paulli M, Strater J, Gianelli U, Rousset MT, Gambacorta M, Orlandi E, et al. Mediastinal B-cell lymphoma: a study of its histomorphologic spectrum based on 109 cases. *Hum Pathol* 1999; 30:178-87.
4. Zinzani PL, Martelli M, Bendandi M, De Renzo A, Zaccaria A, Pavone E, et al. Primary mediastinal large B-cell lymphoma with sclerosis: a clinical study of 89 patients treated with MACOP-B chemotherapy and radiation therapy. *Haematologica*. 2001; 86:187-91.
5. Zinzani PL, Martelli M, Bertini M, Gianni AM, Devizzi L, Federico M, et al. Induction chemotherapy strategies for primary mediastinal large B-cell lymphoma with sclerosis: a retrospective multinational study on 426 previously untreated patients. *Haematologica* 2002; 87:1276-83.
6. Cairoli R, Grillo G, Tedeschi A, Gargantini L, Marengo P, Tresoldi E, et al. Efficacy of an early intensification treatment integrating chemotherapy, autologous stem cell transplantation and radiotherapy for poor risk primary mediastinal large B cell lymphoma with sclerosis. *Bone Marrow Transplant* 2002; 29:473-7.

Guidelines in hematology

Progress in health care requires that the medical education is continued post-doctorally and that appropriate guidelines are prepared and regularly reviewed for diagnosis and treatment. The whole issue is complex. On the one hand it must be under the control of the academic and health authorities, namely Universities, Hospitals, Research Institutes and Professional Orders. On the other hand it requires the active contribution of the scientific and medical community, which is represented by the scientific Societies. Representing the hematological community, the Italian Society of Hematology (SIE), the Italian Society of Experimental Hematology (SIES) and the Italian Group for Stem Cell Transplantation (GITMO) have joined to provide the best available professional and scientific framework for continuing medical education (CME) in hematology and for the preparation and regular revision of guidelines for the main hematological disorders, from anemia and hemorrhagic diseases to leukemia and lymphoma, from diagnosis and conventional treatment to cellular and gene therapy. The first step was the establishment of a permanent committee for the guidelines, which is now served by Sante Tura at University of Bologna and Giovanni Barosi at the IRCCS Policlinico S. Matteo, Pavia. The committee is entrusted to form specific independent subcommittees for the main blood diseases so as to prepare the respective guidelines according to recognized scientific methodologies. The guidelines will be offered to the medical community with the help of the national and regional Health authorities and via Internet, at a site that will be activated before the end of the year and will provide an open forum for interactive discussion. They will also be published, upon independent review, in the Societies' official Journal, which is *Haematologica*. We are happy to welcome in this issue of the Journal the first of these guidelines, which is dedicated to the treatment of myelodysplastic syndromes. Forthcoming guidelines will concern thrombocytopenia, monoclonal gammap-