20. Eapen M, Rocha V, Sanz G, Scaradavou A, Zhang MJ, Arcese W, et al. Effect of graft source on unrelated donor haemopoietic stem-cell transplantation in adults with acute leukaemia: a retrospective analysis. Lancet Oncol. 2010;11(7):653-60.
21. Ferrá C, Sanz J, de la Cámara R, Sanz G, Bermúdez A, Valcárcel D, et al. Unrelated transplantation for poor-prognosis adult acute lymphoblastic leukemia: long-term outcome analysis and study of the impact of hematopoietic graft source. Biol Blood Marrow Transplant. 2010;16(7):957-66.
22. Onishi Y, Sasaki O, Ichikawa S, Inokura K, Katsuoka Y, Ohtsuka Ohba R, et al. Favorable outcome of unrelated cord blood transplantation for Philadelphia chromosome-positive acute lymphoblastic leukemia. Biol Blood Marrow Transplant. 2011;17(7):1093-7.
23. Nishiwaki S, Inamoto Y, Imamura M, Tsurumi H, Hatanaka K, Kawa K, et al. Reduced-intensity versus conventional myeloablative conditioning for patients with Philadelphia chromosome-negative acute lymphoblastic leukemia in complete remission. Blood. 2011;117 (13):3698-9.
24. Horwitz ME. Reduced intensity versus myeloablative allogeneic stem cell transplantation for the treatment of acute myeloid leukemia, myelodysplastic syndrome and acute lymphoid leukemia. Curr Opin Oncol. 2011;23(2):197-202.
25. Marks DI, Wang T, Pérez WS, Antin JH, Copelan E, Gale RP, et al. The outcome of full-intensity and reduced-intensity conditioning matched sibling or unrelated donor transplantation in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia in first and second complete remission. Blood. 2010;116(3):366-74.
26. Mohty M, Labopin M, Volin L, Gratwohl A, Socié G, Esteve J, et al. Reduced-intensity versus conventional myeloablative conditioning allogeneic stem cell transplantation for patients with acute lymphoblastic leukemia: a retrospective study from the European Group for Blood and Marrow Transplantation. Blood. 2010;116(22):4439-43.
27. Mohty M, Labopin M, Tabrizzi R, Theorin N, Fauser AA, Rambaldi A, et al. Reduced intensity conditioning allogeneic stem cell transplantation for adult patients with acute lymphoblastic leukemia: a retrospective study from the European Group for Blood and Marrow Transplantation. Haematologica. 2008;93(2):303-6.
28. Ram R, Storb R, Sandmaier BM, Maloney DG, Woolfrey AE, Flowers MED, et al. Non-myeloablative conditioning with allogeneic hematopoietic cell transplantation for the treatment of high-risk acute lymphoblastic leukemia. Haematologica 2011;96(8):1113-1120.
29. Stein AS, Palmer JM, O'Donnell MR, Kogut NM, Spielberger RT, Slovak ML, et al. Reduced-intensity conditioning followed by peripheral blood stem cell transplantation for adult patients with high-risk acute lymphoblastic leukemia. Biol Blood Marrow Transplant. 2009;15(11):1407-14.
30. Arnold R, Massenkeil G, Bornhauser M, Ehninger G, Beelen DW, Fauser AA, et al. Nonmyeloablative stem cell transplantation in adults with high-risk ALL may be effective in early but not in advanced disease. Leukemia. 2002;16(12):2423-8.
31. Martino R, Giralt S, Caballero MD, Mackinnon S, Corradini P, Fernandez-Aviles F, et al. Allogeneic hematopoietic stem cell transplantation with reduced-intensity conditioning in acute lymphoblastic leukemia: a feasibility study. Haematologica. 2003;88(5):555-60.
32. Bachanova V, Verneris MR, DeFor T, Brunstein CG, Weisdorf DJ. Prolonged survival in adults with acute lymphoblastic leukemia after reduced-intensity conditioning with cord blood or sibling donor transplantation. Blood. 2009;113(13):2902-5.
33. Lee HJ, Thompson JE, Wang ES, Wetzler M. Philadelphia chromosome-positive acute lymphoblastic leukemia: current treatment and future perspectives. Cancer. 2011;117(8):1583-94.
34. Fielding AK. How I treat Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood. 2010;116(18):3409-17.
35. Fielding AK, Buck G, Lazarus H, Litzow MR, Luger S, Marks DI, et al. Imatinib significantly enhances long-term outcomes in Philadelphia positive acute lymphoblastic leukaemia; final results of the UKALLXII/ECOG2993 Trial. Blood. 2010;116:493.
36. Pfeifer H, Goekbuget N, Volp C, Hüttmann A, Lübbert M, Stuhlmann R, et al. Long-term outcome of 335 adult patients receiving different schedules of imatinib and chemotherapy as front-line treatment for Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL). Blood. 2010;116:173.
37. Mizuta S, Matsuo K, Yagasaki F, Yujiri T, Hatta Y, Kimura Y, et al. Pre-transplant imatinib-based therapy improves the outcome of allogeneic hematopoietic stem cell transplantation for BCR-ABL-positive acute lymphoblastic leukemia. Leukemia. 2011;25(1):41-7.
38. Foa R, Vitale A, Guarini A, De Propris MS, Elia L, Cimino G, et al. Dasatinib as first line treatment of adult Ph+ acute lymphoblastic leukemia (ALL) patients. Final results of the GIMEMA LAL1205 study. Blood. 2008;112:305.
39. Rousselot P, Hayette S, Récher C, Leguay T, Salanoubat C, Witz F, et al. Dasatinib (Sprycel®) and low intensity chemotherapy for first-line treatment in elderly patients with de novo Philadelphia positive ALL (EWALL-PH-01): kinetic of response, resistance and prognostic significance. Blood. ASH poster. 2010;116:1204.
40. Ravandi F, O'Brien S, Thomas D, Faderl S, Jones D, Garris R, et al. First report of phase 2 study of dasatinib with hyper-CVAD for the frontline treatment of patients with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia. Blood. 2010;116(12):2070-7.
41. Horwitz ME. Reduced intensity versus myeloablative allogeneic stem cell transplantation for the treatment of acute myeloid leukemia, myelodysplastic syndrome and acute lymphoid leukemia. Curr Opin Oncol. 2011;23(2):197-202.
42. Ribera JM, Oriol A, Gonzalez M, Vidriales B, Brunet S, Esteve J, et al. Concurrent intensive chemotherapy and imatinib before and after stem cell transplantation in newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia. Final results of the CSTIBES02 trial. Haematologica 2010;95(1):87-95.
43. Wassmann B, Bethge W, Bornhauser J, Dengler J, Stadler D. Up-front versus minimal residual disease triggered imatinib after stem cell transplantation for Philadelphia chromosome-positive acute lymphoblastic leukaemia: interim results of a randomized phase III GMALL study. Bone Marrow Transplant. 2009;43(5):S48.
44. Burke MJ, Trotz B, Luo X, Baker KS, Weisdorf DJ, Wagner JE, et al. Allo-hematopoietic cell transplantation for Ph chromosome-positive ALL: impact of imatinib on relapse and survival. Bone Marrow Transplant. 2009;43(2):107-13.
45. Topp MS, Kufer P, Gökbuget N, Goebeler M, Klinger M, Neumann S, et al. Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. J Clin Oncol. 2011;29(18): 2493-8.
46. Fielding AK, Richards SM, Chopra R, Lazarus HM, Litzow MR, Buck G, et al. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. Blood. 2007;109(3):944-950.
47. Oriol A, Vives S, Hernández-Rivas JM, Tormo M, Heras I, Rivas C, et al. Outcome after relapse of acute lymphoblastic leukemia in adult patients included in four consecutive risk-adapted trials by the PETHEMA Study Group. Haematologica. 2010;95(4):589-96.
48. Kantarjian HM, Thomas D, Ravandi F, Faderl S, Garcia-Manero G, Shan J, et al. Outcome of adults with acute lymphocytic leukemia in second or subsequent complete remission. Leuk Lymphoma. 2010;51(3):475-80.

Indolent mantle cell lymphoma

Michelle Furtado and Simon Rule

Department of Haematology, Derriford Hospital, Plymouth, UK.
E-mail: simon.rule@nhs.net

doi:10.3324/haematol.2011.047357

(Related Original Article on page 1121)

Mantle cell lymphoma (MCL) accounts for approximately 6% of all non-Hodgkin's lymphomas[1] and is characterized by the over-expression of cyclin D1 with cell cycle dysregulation, secondary to the genetic abnormality t(11;14)(q13;q32).[2] It often has an aggressive clinical course and is generally associated with a poor prognosis. Although there are a number of treatment options for these patients and initial response rates are

improving, the remissions achieved are generally not durable and, with the possible exception of allogeneic transplantation, no treatment can be considered curative. The multiply-relapsing pattern of behavior in this disease contributes to a widely quoted median survival of 3-5 years.[1] Given its poor prognosis, MCL is usually treated at diagnosis with aggressive chemotherapy but with a median age at presentation in the mid 60s, most patients are not eligible for intensive therapies.

In the last few years there has been recognition that a subset of patients with MCL have a significantly longer survival (often more than 7-10 years) and a more indolent disease course. Two groups have reported on separate cohorts of patients who did not receive up-front chemotherapy at the time of diagnosis but were instead managed with a 'watch and wait' approach.[3,4] Both groups found that this approach did not have adverse effects on survival outcomes, suggesting that if such patients can be reliably identified, chemotherapy for this group, with its attendant morbidity, could reasonably be deferred. Although diagnostic criteria for the identification of these patients are not currently available, there is evolving recognition of clinicopathological differences identifying this group from the group of patients with classical MCL.

It is becoming clear that many, although by no means all, patients with indolent disease present with a leukemic picture rather than nodal disease. Fernandez *et al.*[5] found that while both indolent and classical forms of MCL share a common gene expression profile, which differs from that of other leukemic variants of lymphoid neoplasms, there are significant differences between the two. In particular 13 genes were found to be differentially expressed: all were under-expressed in patients with indolent disease and over-expressed in those with classical disease. *SOX11* is one of these and potentially has an important role in both the pathogenesis of MCL and in the identification of indolent disease.

SOX11 is a single exon gene and codes for one of the three group C Sry-related HMG box proteins (along with SOX4 and SOX12). These proteins are thought to play a significant role in the control of cell differentiation during many developmental processes, key among these being neuronal differentiation.[6] Their developmental necessity is evident from single gene knockout studies showing that Sox4-null and Sox11-null mice cannot survive because of heart outflow tract malformations (they die at embryonic day 14 and just after birth, respectively).[7,8] SOX4 is also required for B lymphocyte differentiation. The role of SOX11 in hematologic development (both normal and malignant) is unclear, although there is emerging evidence for SOX11-responsive genes[9] and a potential tumor suppressor role of SOX11 in MCL.[10]

Cytoplasmic SOX11 may be found to a variable extent in B-cell neoplasms and certain normal adult tissues.[11] Strong nuclear expression of SOX11 (detected by immunohistochemistry) is confined to MCL, lymphoblastic lymphomas (B and T), and some Burkitt's lymphomas with weaker nuclear expression present in hairy cell leukemia.[12]

As well as being of diagnostic value, the distribution of SOX11 staining in MCL may be prognostic, since Wang *et al.* showed that non-nuclear staining is associated with impaired overall survival.[13] This potentially contradicts the findings from the study by Fernandez *et al.* in which non-nuclear staining was found in patients with indolent MCL, who had a better overall survival.[5]

The work by Fernandez *et al.*[5] also showed that 70% of cases of indolent MCL have highly mutated (>5%) *IGVH* genes. Although this mutation rate is much higher than that seen in classical MCL (~20%) the significance of this remains controversial, with one group reporting no clinical difference[14] but another group reporting an overall survival advantage.[15] Orchard *et al.* identified a higher incidence of mutated *IGVH* genes in leukemic rather than nodal MCL, alongside a more indolent course in some of these leukemic patients.[16]

Gene expression analysis applied to MCL has provided further prognostic information by way of a proliferation gene expression signature.[17] By assigning a value to each of 20 proliferation genes that were differentially expressed among MCL cases a proliferation signature average was calculated and found to correlate inversely with survival. The cohort with low proliferation gene scores had a similar survival to that of the patients with indolent MCL identified in other studies. A more pragmatic way of assessing proliferation is through Ki-67 staining. This provides prognostic information and has been validated within the MCL-specific International Prognostic Index (MIPI) score.[18]

In a study published in this issue of the journal, Ondrejka *et al.* investigated a cohort of patients with leukemic MCL exhibiting an indolent disease course.[19] They retrospectively analyzed archived samples and data from eight patients who presented with leukemic MCL over a 10-year period. All these cases were found incidentally in asymptomatic patients with lymphocyte counts varying between 4.5 and 14.2×10^9/L and all were t(11:14)-positive. These patients had no progression or very slowly rising lymphocyte counts and only two required any form of treatment as of the time of analysis. All the available bone marrow biopsies from the time of diagnosis showed low level MCL involvement detectable by immunohistochemistry. When examined by flow cytometry a significant proportion had a subset of CD23 positive cells (usually negative in MCL) and the majority of the patients in the study showed kappa light chain restriction, as opposed to the more typical lambda light chain restriction usually found in MCL.

The finding of kappa light chain restriction in the majority of these patients is interesting and may lead to further insights into the development of different subsets of MCL, due to the differences in the timing of kappa and lambda light chain rearrangement during B-cell development.

Given the previous reports regarding the potential prognostic value of SOX11 expression, immunolabeling of SOX11 was performed. The results concur with other studies examining leukemic MCL with an absence of staining in the majority of patients (one patient had some very minor nuclear staining), compared to the strongly positive staining observed in conventional nodal MCL (P=0.00001).

With this study, Ondrejka *et al.* provide further evidence for both the potential prognostic use of SOX11 and the existence of a subset of MCL patients with very indolent disease. However, by excluding patients with lymphadenopathy, splenomegaly and gastrointestinal symptoms, their study omitted a potentially large group of patients with indolent MCL. From their own data, only 3%

of patients with MCL have a leukemic form, while the unselected cohorts studied by Martin *et al.*[3] and Eve *et al.*[4] indicated that up to 30% of all MCL may exhibit an indolent behavior.

It is possible that while leukemic MCL was traditionally associated with a poorer prognosis,[20] the better overall survival of the patients seen in the more recent studies may be due to changes in entry criteria. As postulated by Ondrejka *et al.*, some of the cases of leukemic MCL may in fact be considered a form of MCL-type monoclonal B-cell lymphocytosis rather than MCL, and that many more of these patients might be detected if all patients with monoclonal B-cell lymphocytosis are screened for t(11:14)/*IGH@-CCND1*. This may explain the heterogeneity seen within patients in the non-nodal group in the study by Orchard *et al.* who found increased variability in karyotype complexity and *IGVH* mutation status in leukemic compared to nodal MCL.[16]

Now that a reliable SOX11 antibody is available this may become incorporated into routine MCL diagnosis especially as SOX11 can identify the rare cyclin D1-negative patients.[21] The differences reported regarding the prognostic value of nuclear SOX11 staining could be reconciled if nodal indolent MCL is considered as an entity separate from, but related to leukemic indolent MCL. The report by Wang *et al.* showing a shorter overall survival in patients with non-nuclear SOX11 staining[13] did not describe the population of patients, so it may be that SOX11-negative *nodal* MCL behaves differently from SOX11-negative *leukemic* disease.

While there is no doubt that indolent MCL exists, and it is well recognized within patients presenting with non-nodal, leukemic disease, it is likely that this is not the only clinical scenario. *SOX11* and other genes are likely to become useful in the identification of these patients at diagnosis and this will ultimately provide clinicians with the confidence to explore less intensive treatment approaches.

Dr Simon Rule and Dr Michelle Furtado are Consultants, Haematologists and Honorary Readers, Department of Haematology, Derriford Hospital, Plymouth UK.

Financial and other disclosures provided by the author using the ICMJE (www.icmje.org) Uniform Format for Disclosure of Competing Interests are available with the full text of this paper at www.haematologica.org.

References

1. Swerdlow S, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. International Agency for Research on Cancer (IARC); 2008.
2. Raffeld M, Jaffe ES. Bcl-1, t(11;14), and mantle cell-derived lymphomas. Blood. 1991;78(2):259-63.
3. Martin P, Chadburn A, Christos P, Weil K, Furman RR, Ruan J, et al. Outcome of deferred initial therapy in mantle-cell lymphoma. J Clin Oncol. 2009;27(8):1209-13.
4. Eve HE, Furtado MV, Hamon MD, Rule SAJ. Time to treatment does not influence overall survival in newly diagnosed mantle cell lymphoma. J Clin Oncol. 2009;27(32):e189-90.
5. Fernàndez V, Salamero O, Espinet B, Solé F, Royo C, Navarro A, et al. Genomic and gene expression profiling defines indolent forms of mantle cell lymphoma. Cancer Res. 2010;70(4):1408-18.
6. Haslinger A, Schwartz T, Covic M, Chichung Lie D. Expression of SOX11 in adult neurogenic niches suggests a stage-specific role in adult neurogenesis. Eur J Neurosci. 2009;29(11):2103-14.
7. Ya J, Schilham MW, Boer PA de, Moorman AF, Clevers H, Lamers WH. Sox4-deficiency syndrome in mice is an animal model for common trunk. Circ Res. 1998;83(10):986-94.
8. Sock E, Rettig SD, Enderich J, Bösl MR, Tamm ER, Wegner M. Gene targeting reveals a widespread role for the high-mobility-group transcription factor Sox11 in tissue remodelling. Mol Cell Biol. 2004;24(15):6635-44.
9. Wang X, Björklund S, Wasik AM, Grandien A, Andersson P, Kimby E, et al. Gene expression profiling and chromatin immunoprecipitation identify DBN1, SETMAR and HIG2 as direct targets of SOX11 in mantle cell lymphoma. PloS one. 2010;5(11):e14085.
10. Gustavsson E, Sernbo S, Andersson E, Brennan DJ, Dictor M, Jerkeman M, et al. SOX11 expression correlates to promoter methylation and regulates tumor growth in hematopoietic malignancies. Mol Cancer. 2010;9:187.
11. Ek S, Dictor M, Jerkeman M, Jirström K, Borrebaeck CA. Nuclear expression of the non B-cell lineage Sox11 transcription factor identifies mantle cell lymphoma. Blood. 2008;111(2):800-5.
12. Dictor M, Ek S, Sundberg M, Warenholt J, Gyorgy C, Sernbo S, et al. Strong lymphoid nuclear expression of SOX11 transcription factor defines lymphoblastic neoplasms, mantle cell lymphoma and Burkitt's lymphoma. Haematologica. 2009;94(11):1563-8.
13. Wang X, Asplund AC, Porwit A, Flygare J, Smith CI, Christensson B, et al. The subcellular Sox11 distribution pattern identifies subsets of mantle cell lymphoma: correlation to overall survival. Br J Haematol. 2008;143(2):248-52.
14. Kienle D, Kröber A, Katzenberger T, Ott G, Leupolt E, Barth TFE, et al. VH mutation status and VDJ rearrangement structure in mantle cell lymphoma: correlation with genomic aberrations, clinical characteristics, and outcome. Blood. 2003;102(8):3003-9.
15. Lai R, Lefresne SV, Franko B, Hui D, Mirza I, Mansoor A, et al. Immunoglobulin VH somatic hypermutation in mantle cell lymphoma: mutated genotype correlates with better clinical outcome. Mod Pathol. 2006;19(11):1498-505.
16. Orchard J, Garand R, Davis Z, Babbage G, Sahota S, Matutes E, et al. A subset of t(11;14) lymphoma with mantle cell features displays mutated IgVH genes and includes patients with good prognosis, nonnodal disease. Blood. 2003;101(12):4975-81.
17. Rosenwald A, Wright G, Wiestner A, Chan WC, Connors JM, Campo E, et al. The proliferation gene expression signature is a quantitative integrator of oncogenic events that predicts survival in mantle cell lymphoma. Cancer Cell. 2003;3(2):185-97.
18. Hoster E, Dreyling M, Klapper W, Gisselbrecht C, Hoof A van, Kluin-Nelemans HC, et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. Blood. 2008;111(2):558-65.
19. Ondrejka SL, Lai R, Kumar N, Smith SD, Hsi ED. Indolent mantle cell leukemia: clinicopathological variant characterized by isolated lymphocytosis, interstitial bone marrow involvement, κ light chain restriction, and good prognosis. Haematologica. 2011;96(8)1221-7.
20. Ferrer A, Salaverria I, Bosch F, Villamor N, Rozman M, Beà S, et al. Leukemic involvement is a common feature in mantle cell lymphoma. Cancer. 2007;109(12):2473-80.
21. Mozos A, Royo C, Hartmann E, De Jong D, Baro C, Valera A, et al. SOX11 expression is highly specific for mantle cell lymphoma and identifies the cyclin D1-negative subtype. Haematologica. 2009;94(11):1555-62.