W17: Philadelphia chromosome positive acute lymphoblastic leukaemia arising in Waldenstrom's macroglobulinaemia

Niamh Appleby[1,2,3], David Bruce[1,2,3], Graham Collins[3], Robert Danby[3] Chris Hatton[3], , Andrew Peniket[3], Gareth Turner[4], Daniel Royston[4] Jaimal Kothari[3]

1. Oxford Molecular Diagnostic Centre, Molecular Haematology, John Radcliffe Hospital, Oxford, OX3 9DU
2. Department of Oncology, University of Oxford,
3. Clinical Haematology, Oxford University Hospitals NHS Foundation Trust, Cancer and Haematology Centre, Churchill Hospital, Old Road Campus, Oxford
4. Haematopathology, John Radcliffe Hospital, OX39DU

We present a 66-year-old woman with marrow-based BCR-ABL associated B acute lymphoblastic leukaemia (Ph+ B-ALL) arising 14 years following diagnosis of lymphoplasmacytic lymphoma (LPL).

The patient presented with anaemia and an IgM kappa paraprotein in 2003. Bone marrow examination showed a diffuse infiltrate of CD79a+ CD20+ CD10- CD5- CyclinD1- kappa-restricted small B-cells with lymphoplasmacytic morphology.

Single-agent chlorambucil in 2005 resulted in a disease control for five years. At first relapse in 2010, she received rituximab and chlorambucil. The disease again progressed in 2013 and the patient attained a PR on rituximab and bendamustine on the MABCUTE trial.

Four years later, the patient presented with neuropathic symptoms. The full blood count was haemoglobin 115g/dL, leukocytes $4.21x10^9$/L, lymphocytes1.9 $x10^9$/L, neutrophils $1.41x10^9$/L and platelets $81x10^9$/L and IgM 5.9g/L. Bone marrow examination revealed a diffuse infiltrate of medium sized blasts expressing TdT+ CD19+ CD79a+ CD10+ BCL2+ and immunonegative for CD20, CyclinD1 and MUM1/IRF4. The BCR-ABL fusion transcript was detected, consistent with a diagnosis of B-ALL with t(9:22)(q34:q11.2); BCR-ABL1. Karyotyping showed 46,XX, -2+?8, t(9;22)(q34;q11),+der(14_t(2:14)(p13;q32)[4]/46,xx[2]/

Our patient commenced induction chemotherapy with the UK-ALL 60+ protocol and imatinib (tyrosine kinase inhibitor). Marrow following induction showed morphological remission but the t(9:22) translocation remained detectable in 5/200 cells examined. After 3 months of imatinib, BCR:ABL transcript ratio was 0.034%.

Six months following the diagnosis of Ph+ B-ALL, her neuropathic symptoms progressed, consistent with an infiltrative plexopathy affecting the brachial and lumbosacral plexuses. Superficial peroneal nerve biopsy showed no lymphoid infiltrate or amyloid deposition but bone marrow examination revealed a nodular infiltrate of small lymphoplasmacytic cells expressing CD20+ CD79a+ and negative for blast markers, confirming LPL relapse. Clonal immunoglobulin heavy chain gene rearrangements were detectable.

Currently, the patient is receiving ibrutinib 420mg (oral Bruton's tyrosine kinase inhibitor) for relapsed LPL in combination with imatinib 400mg daily. Her neuropathic symptoms are improving. Her full blood count shows haemoglobin 106g/L, lymphocytes $2.17x10^9$/L and platelets 140 $x10^9$/L and her IgM kappa paraprotein declines steadily. Her recent BCR:ABL transcript ratio was 0.0038%.

Sequential peripheral blood and marrow samples were interrogated using our 21 gene next-generation sequencing targeted panel which covers clinically significant driver genes in LPL. Where available, paired plasma cell-free DNA samples were examined for somatic mutations in the circulating tumour DNA.

Acute leukaemia complicating LPL is extremely rare. Literature review identified two previous cases of B-ALL following LPL, neither of which report molecular findings or clinical outcomes [1, 2].

References:

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2 R. A. Madan, V. T. Chang, C. Yook, F. K. Baddoura, S. Srinivas, and B. Kasimis, 'Waldenstrom's Macroglobulinemia Evolving into Acute Lymphoblastic Leukemia: A Case Report and a Review of the Literature', *Leukemia,* 18 (2004), 1433-35.