Transformation of CLL (Richter’s Syndrome and Prolymphocytic transformation)

- The titles in this series are intended to provide general information about the topics they describe.
- In many cases the treatment of individual patients will differ from that described.
- At all times patients should rely on the advice of their specialist who is the only person with full information about their diagnosis and medical history.

B-cell prolymphocytic transformation and Richter’s syndrome are relatively rare conditions which arise in a small proportion of patients with Chronic Lymphocytic Leukaemia (CLL). Prolymphocytic leukaemia can also occur as a separate disease unrelated to pre-existing CLL. There is a Leukaemia & Lymphoma Research booklet available on CLL.

What is prolymphocytic leukaemia?

Prolymphocytic leukaemia (PLL) is a rare form of lymphocytic leukaemia accounting for about 1% of all CLL cases. Most PLL patients have this disease when first seen (de-novo PLL) but some will have had CLL which has transformed into a disease resembling PLL.

The abnormal white blood cells seen in PLL are called prolymphocytes. The diagnosis is PLL rather than CLL if more than about half of the leukaemic cells are prolymphocytes. If there are prolymphocytes present but these make up less than half of all the abnormal cells the condition is called mixed CLL/PL.

What is Richter’s Syndrome?

Richter’s syndrome is the situation where a patient who has CLL then develops a lymphoma. Laboratory tests show that usually the lymphoma comes from the same population of cells as the leukaemia but the lymphoma may arise independently. In the latter case the lymphoma could be regarded as a second cancer arising by chance.

Causes

CLL, PLL and Richter’s syndrome are all diseases of later life. Patients may have a diagnosis of PLL when they are first seen, but this also occurs, like Richter’s syndrome, in patients who already have CLL. All of the diseases are seen more commonly in men than in women.

There are no obvious causes for the transformation of CLL to PLL or
Richter’s syndrome. The causes of de-novo PLL are not known, but the risk factors are thought to be the same as for CLL.

About 10% of patients who have CLL will have their illness transform into a disease resembling prolymphocytic leukaemia. As in CLL, the malignant cells in PLL and Richter’s syndrome are B cells. Another condition called T-cell PLL has no relation with CLL or B-cell PLL and tends to progress more quickly than the B cell conditions.

There is no clear link between previous treatment for CLL and transformation into PLL or Richter’s syndrome. The age of patients with an initial diagnosis of PLL is on average slightly older than for CLL patients. It is possible that many of these patients may have had undiagnosed CLL, possibly for many years, and that this had already transformed into PLL by the time they were diagnosed.

What are the signs & symptoms?

A patient with PLL will typically have a very large spleen and a very high white count. Most patients do not have enlarged lymph nodes. Non-specific symptoms like tiredness and weight loss are common.

Patients with Richter’s Syndrome typically present with increasing enlargement of lymph nodes, liver and spleen, fever, abdominal pain and weight loss. They often have marked anaemia and low platelet counts leading to bleeding/bruising.

How are the conditions diagnosed?

In the laboratory the appearance of prolymphocytes in the blood film is quite distinctive and the diagnosis is usually obvious.

Patients may be asked to have a bone marrow sample taken. This involves obtaining a small amount of marrow from inside the bone with a needle, and a tissue sample which will show if the structure of the bone marrow is normal or changed. The first is known as a bone marrow aspirate, the second as a bone marrow trephine. The samples are usually obtained from the back of the hip bone, although the breast bone (sternum) may be used instead for bone marrow aspirates (but not for trephines). The procedure causes some discomfort but does not take very long. The procedure is usually carried out with sedation as well as local anaesthetic.

Richter’s Syndrome patients will have enlarged lymph nodes. Samples are taken from these nodes for laboratory tests. The form of lymphoma is most often either large-cell or immunoblastic lymphoma.

How are the conditions treated?

All patients with PLL will need treatment. This differs from CLL in which many patients do not require treatment.

Unfortunately PLL tends to progress more quickly than CLL
and responds less well to treatment. The response to treatment and overall survival tends to be somewhat better in those cases which arise in patients who did not previously have CLL. The median survival in CLL is about eight years and in ‘new’ cases of PLL it is about three to five years. It is important to stress that median survival means that half of all patients will survive longer than this, possibly many years longer.

The new nucleoside analogue drugs fludarabine (Fludara™) and chlorodeoxyadenosine (Cladribine™) have shown promising results in patients with B-cell PLL. Some patients with B PLL and Richter’s syndrome benefit from combination chemotherapy such as CHOP (which involves the four drugs cyclophosphamide, doxorubicin, vincristine and prednisone). A highly targeted drug called rituximab may be used in addition to CHOP.

In the unrelated condition T-cell PLL treatment with the nucleoside analogue deoxycoformycin (Pentostatin™) and a monoclonal (very specific) antibody called CAMPATH-1H have resulted in complete remissions and long survivors. A minority of patients have, after complete remission, received an autologous transplant with their own bone marrow or peripheral blood stem cells.

What is the prognosis?
See above.