Lymphoma, Leukaemia and Myeloma
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Lymphoma, leukaemia and myeloma are cancers of the blood cells or bone marrow. The outlook has improved substantially for these cancers. Some are curable- the cancer has gone. Others are not curable but are treatable and can be managed as a chronic condition for many years or decades. This talk, part of a series on major cancers, will provide an overview of these important diseases. This serves as notes on subjects covered rather than a transcript of the lecture.

To understand these cancers, we need to understand what blood does. White blood cells fight infection; if they are not working effectively people can get repeated infections. Red cells transport oxygen and if they are reduced leading to anaemia this may lead to breathlessness and tiredness. Platelets are central to clotting and if platelet counts are low people may experience bleeding or bruising. These are common symptoms of several of these cancers.

Different types of lymphoma and leukaemia occur over the age spectrum from early childhood to late old age whilst myeloma is usually a disease of later age. To get a sense of scale, in the UK there are around 10,000 new cases of leukaemia, 2000 cases of Hodgkin lymphoma, 14,000 cases of non-Hodgkin lymphoma and around 5800 cases of myeloma each year. Children rarely get cancers but among children who do lymphoma and leukaemia are particularly important.

In the solid tumours discussed so far in this lecture series including breast, prostate, lung and bowel cancer the key to a good outcome is often identifying a very local cancer and treating it before it becomes widespread with disseminated disease almost invariably signifying less good outcomes. Leukaemia, lymphoma and myeloma should be seen as disseminated diseases from the beginning. The outlook can be very good in these cancers despite this. Surgery, central to the treatment of early cancer most for solid tumours has relatively little role to play but drugs are central to treatment in almost all cases.

The mainstay of treatment has been, and for many of these diseases still is, cytotoxic chemotherapy. The basic mechanisms of chemotherapy are simple. They can kill any cell that is dividing and since cancer cells are dividing rapidly, they are usually more sensitive and slower to recover than normal cells. Chemotherapy is given in combinations: single drugs alone often lead to resistance and then relapse. They are usually given in cycles separated over time. Chemotherapy, much of which was developed in the 1950s and 60s has arisen from multiple origins. They can work along the whole pathway as cells divide.

Radiotherapy it is used in a minority of cases in several leukaemias and lymphomas. Lymphoma tends to be very radiosensitive. Stem cell transplantation is when the bone marrow is damaged by drugs or radiotherapy in the process of eliminating cancer cells. They can be re-seeded by the stem cells usually of the patient themselves, or of a donor.

Lymphoma

Lymphomas are cancers of the lymphatic system and lymphocytes. Lymphatics drain fluid and waste and help fight infection with lymphocyte white cells. It is divided into Hodgkin and non-Hodgkin lymphoma. There are many types of lymphoma so this only acts as an overview.

Hodgkin lymphoma was first described by Thomas Hodgkin in 1832, and a key finding was the Reed-Sternberg cell by Dorothy Reed. It is most commonly identified by lymph nodes being newly enlarged especially in the neck and shoulders, but can also include night sweats, weight loss, fatigue, fever and itching, also known as B symptoms. There are two peaks in age; late adolescence/early adulthood and older age. When lymphoma is suspected investigations include biopsy of the lymph node and radiology in particular PET/CT scans. How extensive the lymphoma is and whether it has spread to both sides of the diaphragm are important for staging. Treatment consists of chemotherapy in almost all cases and radiotherapy in some. In a few cases of relapse stem cell transplant maybe used. Hodgkin lymphoma now has very good survival. 75% will survive more than 10 years.

In common with most lymphomas, leukaemias and myeloma there is very little modifiable risk for Hodgkin lymphoma. There does appear to be a strong association with Epstein-Barr virus, and it is possible that prevention of this through vaccination might reduce the risk, but this is unproven.

Non-Hodgkin lymphoma

There are many types of non-Hodgkin lymphoma. The great majority arise from B cells. They are often divided into fast-growing (high-grade) and slow growing (low-grade).

For *high-grade lymphoma* the most common symptoms are new swollen lymph glands that don't go down after a couple of weeks. They are usually not painful and are common in the groin, armpit or neck. This is most common in older people. Diagnosing is usually by biopsy with PET/CT for staging. For most high-grade lymphomas the aim of treatment is complete remission (cure). The basis of treatment is chemotherapy, most commonly the CHOP regimen.

Additionally, CD20 antibody therapy with Ritixumab can be used. Targeted therapies using antibodies are increasingly used. Ritixumab is an example of the monoclonal antibody against CD20, found on B cells. By binding to the cells, it attracts the immune system to attack the cells.

In children the commonest non-Hodgkin lymphoma is Burkitt lymphoma. In the UK it is rare and of the sporadic type but in Africa it is more common in areas where EBV and malaria overlap. Treatment of Burkitt's is a combination of chemotherapy and targeted therapy. Survival for limited stage Burkitt lymphoma is over 90% and for advanced stage still 80 to 90%.

Low-grade lymphoma is generally more slowly growing and most common in those aged 60 to 90. It can present with enlarged lymph nodes or B symptoms. It can also be diagnosed incidentally after blood tests for another reason. Although full remission can occasionally occur the main aim is control. People can live for many years with low-grade lymphoma receiving intermittent treatment; 55% survive 10 years or more. They may not need treatment initially but only active monitoring. Treatment usually involves chemotherapy and targeted CD20 antibodies may be used for maintenance therapy.

Leukaemias

Leukaemias are cancers of the white blood cells. They can have acute (rapid) and chronic (slow) onset. Separately they can come from a lymphocytic cell or a myeloid cell.

Chronic lymphocytic leukaemia (CLL) occurs mainly in people over 60. People suffering from this have both too many B lymphocytes which may crowd out other cells in the bone marrow, and the lymphocytes do not work well. Therefore, it can lead to increased infections, tiredness, bleeding/bruising and swollen lymph glands. Early disease with minimal symptoms may not need treatment. The prognosis for CLL is around 85% survive five years or more in the UK. Certain genetic mutations are associated with better or less good survival. In people with early disease no treatment may be best. In more advanced disease the aim is to control, not cure. Some combination of targeted therapies and chemotherapy will be used.

Chronic myeloid leukaemia (CML) is much rarer. There is much improved outlook over time with around 75% reduction in mortality since the 1970s. People with CML have the Philadelphia chromosome which makes cells produce a protein, tyrosine kinase, which encourages leukaemia cells to multiply. The development of tyrosine kinase inhibitors has transformed the outlook (at a substantial cost to the health service).

Acute myeloid leukaemia (AML) can occur in children and older adults. With chemotherapy and more advanced cases stem cell transplant survival in children is much improved with greater than 65% over five years. There is a lower survival rate in those over 65 years.

Acute lymphoblastic leukaemia (ALL) is rarer and is mainly a disease of children. 2 to 5 years is the most common age develop to it and it is rare after 24 years. Outlook is good for most children and in those age 14 or under more than 90% survive more than five years. Chemotherapy is used to achieve remission and the best treatment is strongly influenced by genotype. Chemotherapy may be used for some years to prevent relapse. A major scientific advance is CAR-T therapy. T cells are removed from the blood, programmed to recognise the cancer by inserting receptors and then reinserted into the blood where they attack the cancer.

<u>Myeloma</u>

At the other end of the age spectrum is myeloma, also known as multiple myeloma. It is very rare in those under 40 years and is mainly a cancer of older age. It is a cancer of plasma cells that usually produce antibodies. By displacing other bone marrow cells, it can cause anaemia and infections. The excess immunoglobulin protein can cause ‘sticky’ blood and can lead to a higher risk of kidney damage and clots. The bone can become eroded from the inside leading to fractures, bone pain and too much calcium in the blood.

Not everybody with myeloma needs immediate treatment and the aim in most people is long-term control and reduction of symptoms, not cure. Myelomas are relapsing remitting diseases with periods of activity and periods of relative inactivity and treatments are given when relapses occur. More aggressive treatments in younger patients may include stem cell transplantation. Myeloma survival is steadily improving and over 80% are alive a year after diagnosis and over 50% alive five years later.

Overall, the outlook for lymphoma, leukaemia myeloma has improved substantially. Some are curable, others are treatable and can be managed as a chronic condition for many years or decades. Genotyping to guide of treatment, use of targeted therapy and highly effective (and expensive) treatments like CAR-T will continue to improve survival and reduce side effects.