Pathological Condition: Multiple Myeloma

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1. Introduction

Multiple myeloma is an uncurable blood cancer that originates in the plasma cells located in the bone marrow. This plasma cell disorder has a ratio of 58% male to 42% female and it is generally a disease of older age, however it can be found in people as young as thirty (See figure 1). It tends to be more aggressive when the patient is younger. Myeloma is a rare condition as it constitutes only 1% of malignancies and it is a slightly higher incidence in Afro-Caribbean populations (Kazandjian, 2016).

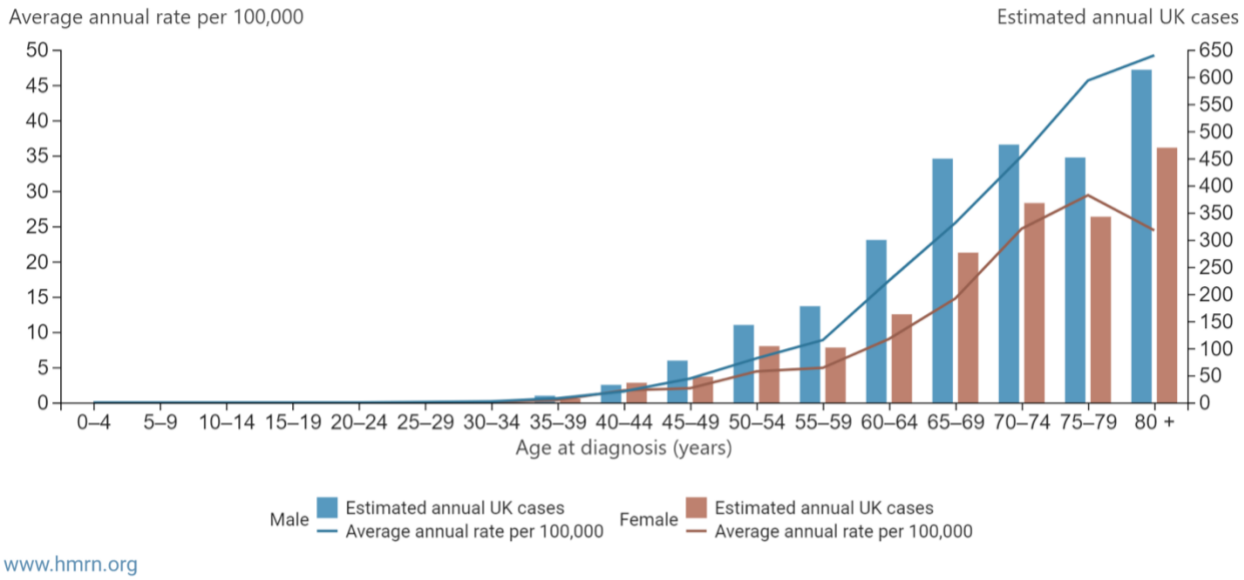


Figure 1: a graph showing myeloma incidence by age group. (The Haematological Malignancy Research Network (HMRN), 2022).

The bone marrow is found in the centre of bones, and it is where most blood cells such as white blood cells, red blood cells and platelets are generated. Plasma cells are derived from the lymphoid stem cells. The lymphoblast matures and it generates B cells. Some of these B cells are selected to become memory B cells after exposure to infection, which then become plasma cells. Plasma cells get transported back to the lymph nodes and spleen to finally migrate to the bone marrow. There the plasma cell function and survival are protected by the unique microenvironments that allows these cells to continue generating antigen-specific antibody even after the depletion of memory B cells (Pinto et al., 2013) (Allman & Northrup, 2010). There are less than 1% plasma cells in the bone marrow (Berenson, 2022).

Plasma cells produce antibodies called immunoglobins. Monoclonal proteins are a type of immunoglobulin produce by a single clone of plasma cells commonly found in multiple myeloma. The

immunoglobulins (Igs) released by plasma cells are composed of heavy and light chains (see figure 3). There are several types:

- Heavy chains: G, A, D, E, M. Most common one is G (IgG).
- Light chains: kappa or lambda.

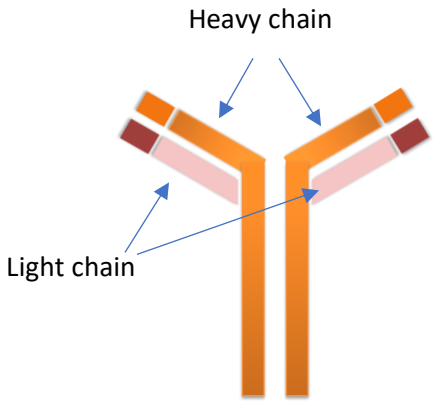


Figure 2: antibody produced by plasma cells called immunoglobulin. The pink area is the light cain and the orange area are the heavy chains.

The plasma cells produce both chains separately and then are assembled inside the cell to generate the antibody. They tend to produce more light chains than they do heavy chains and consequently, there is a slight excess of light chains. This is useful to measure the kappas and lambdas when performing the serum free light chains test that will be mentioned in the *testing section*. The overproduction of light chains cause problems with kidneys in myeloma because the light chains can hinder blood filtration (Pinto et al., 2013). There are four types of plasma cell disorders regarding myeloma (See Figure 3) (Rajkumar, 2016).

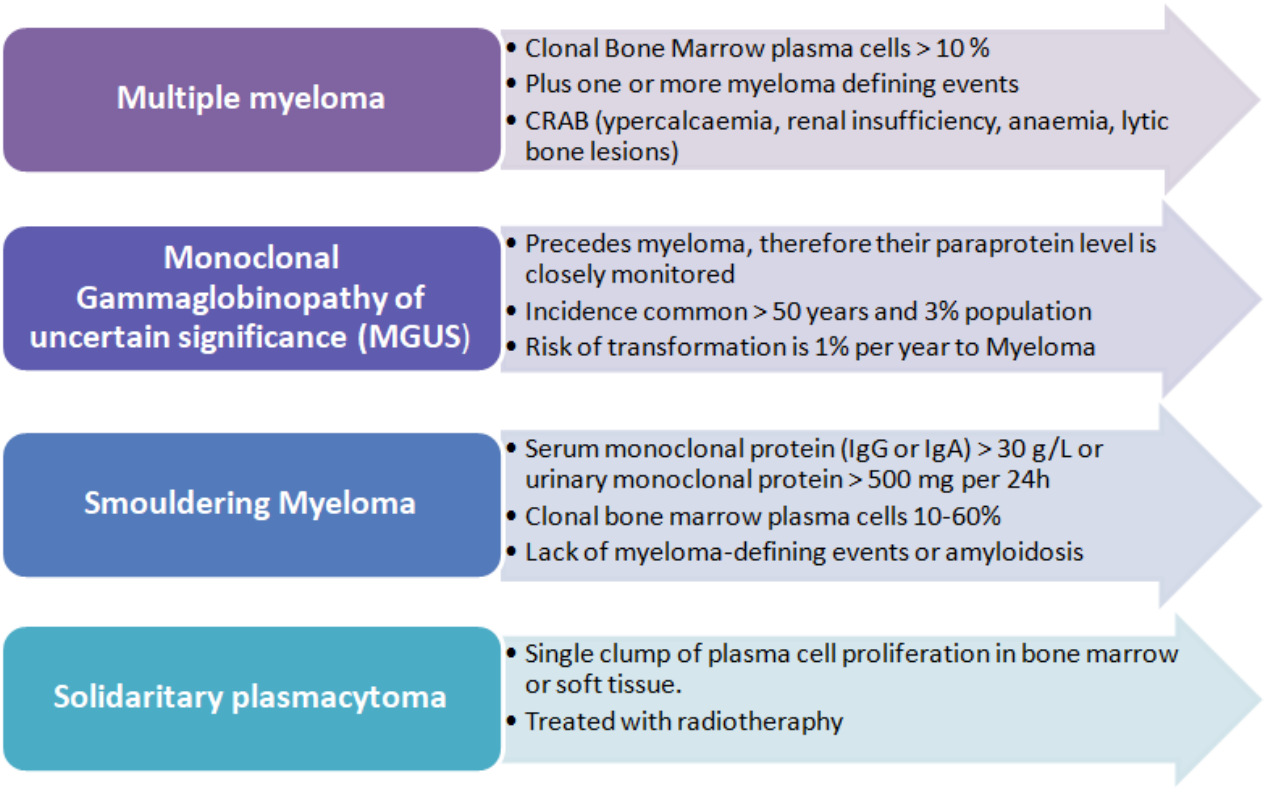


Figure 3: Four types of plasma disorders found in the human body (Rajkumar et al., 2014).

2. Initial investigation

The clinical manifestations of myeloma can be very broad, and it is often discovered when they go to their GP due to other clinical reasons such as back pain. Non-specific symptoms may be associated to non-cancerous diseases. However, due to the nature of this condition, it is critical that the possibility of multiple myeloma is taken into consideration (Myeloma UK, 2018).

It is essential to obtain an early diagnosis of myeloma as it has an impact on survival. Patients that are diagnosed by their GP referral have 26 % higher chance of a better one-year survival compared to those who are diagnosed via emergency presentation (National Cancer Intelligence Network, 2016). However, myeloma patients usually experience a late diagnosis due to the non-specific and vague nature of symptoms. These patients are likely to have undergone various prior GP consultations (Abel et al., 2017). Consulting with the patient early on facilitates prompt identification of typical red flags of myeloma and reduces the probability of an emergency presentation (Myeloma UK, 2018).

Typically, the GP will take blood samples to do general basis screening tests like U&E, FBC, glucose and LFT. These results will then suggest referring the patient to a medical team. When the medical team has a suspicion of myeloma, such as anaemic results from a routine FBC, it is crucial to take further investigative tests such a myeloma screen. This consists of FBC, U&E, calcium test, X-rays and PEPH (Sive et al., 2021).

3. Clinical manifestation

The results of the tests carried out by the medical team will indicate the patient's clinical manifestations of the condition. The most common one is CRAB (Hypercalcaemia, renal insufficiency, anaemia, bone lesions) (See figure 4).

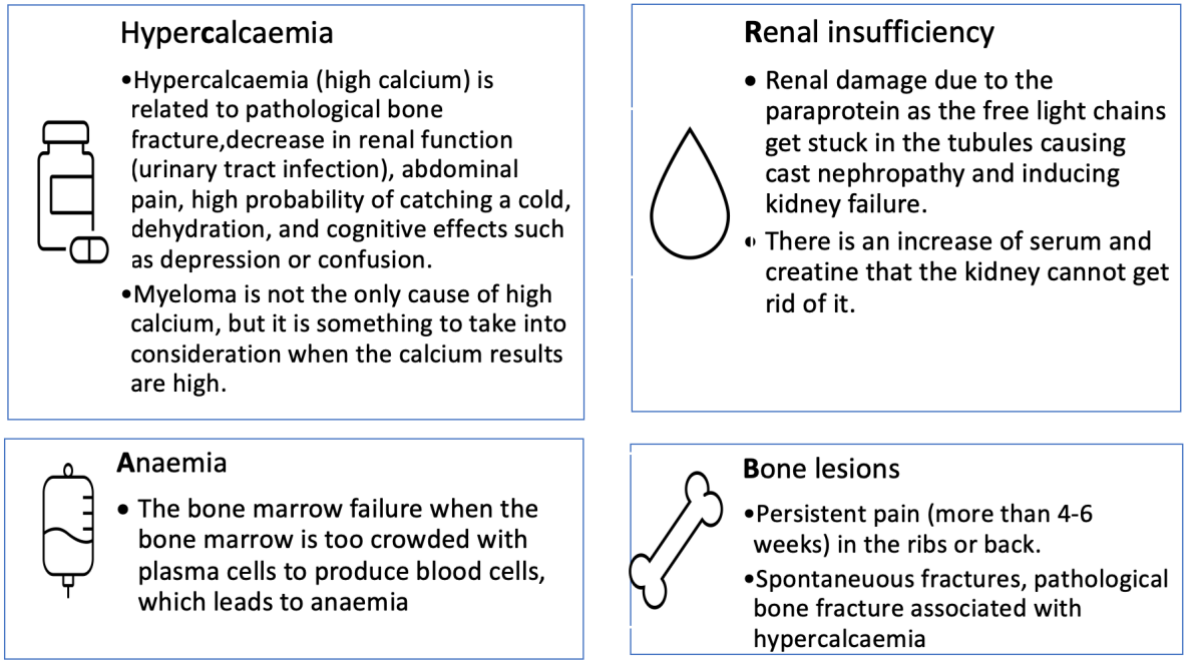


Figure 4: four main clinical manifestation for multiple myeloma (Myeloma UK, 2021).

Other clinical manifestations to consider:

- Amyloid disease: amyloid is an abnormal protein that can be deposited in different organs like the heart and kidney causing problems with their function level (Myeloma UK, 2023).
- Approximately 2% of the cases have hype viscosity syndrome. The excess of the paraprotein make the blood stickier. However, the size of the immunoglobin is not big enough to be a problem whenever the total protein count is not massively high. This manifests with symptoms like headaches, nosebleeds, and visual changes (Myeloma UK, 2021).
- Spinal cord compression can happen when a lesion is present at the bottom of the spinal cord, more specifically at the cauda equina, where many plasma cells are present, and the bone is swelling. The nerves can end up being pushed leading to problems such as bowel and bladder issues. This will be treated as a medical emergency as the patient does not have proper renal function and cannot walk due to the numbness in the legs (Myeloma UK, 2021).
- Ease of having recurrent infections (NHS choices, 2021).
- Lytic lesions on CT and PET suggest that a specific part of the bone has been destroyed (Myeloma UK, 2023).
- Other symptoms such as breathlessness with no explanation, generally feeling unwell including weight loss and fatigue, and peripheral neuropathy without explanation (NHS choices, 2021).

Even though the symptoms can be very broad, there are different symptoms that whenever they arise in combination can have a positive predictive value (PPV) higher than 10 for myeloma (See figure 5) (Shephard et al., 2015)).

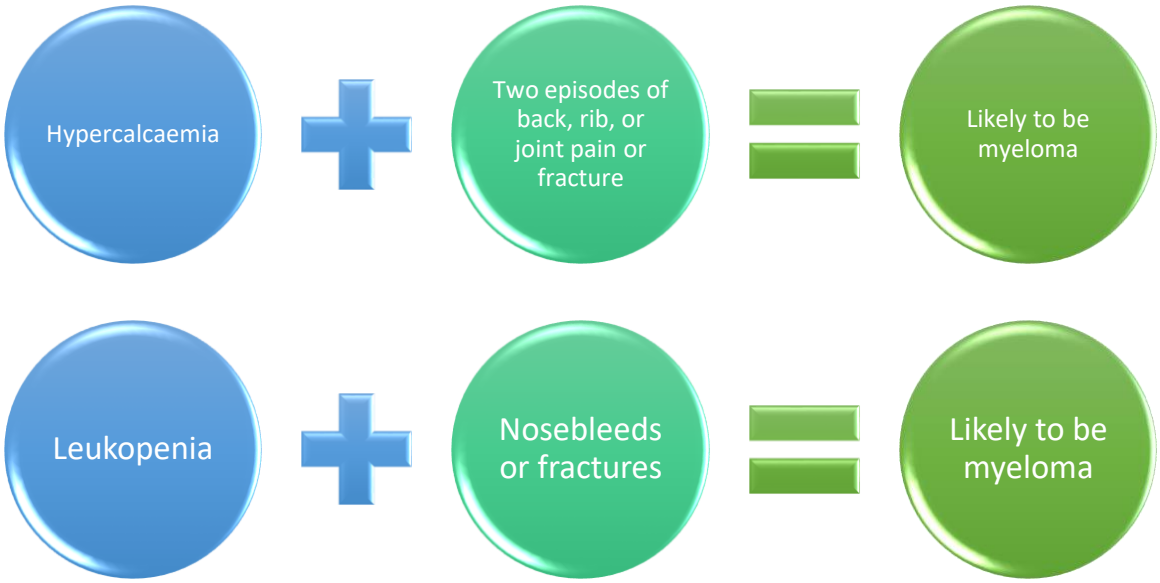


Figure 5: combination of symptoms that usually lead to myeloma (Myeloma UK, 2021).

4. Diagnosis

4.1 Chemistry tests

4. 1.1 Serum

4.1.1.1 Serum Protein Electrophoresis

The test is performed to detect the presence of paraprotein. In our body, there are G, A, D, E, M immunoglobulins that float around and react to specific antigens or infections. Usually, people have only one type of abnormal immunoglobulin, which is produced by a group of affected plasma cells known as paraprotein (Myeloma UK, 2021). In individuals with myeloma, the abnormal plasma cells become genetically mutated and start producing a specific type of immunoglobulin, leading to an increase in paraprotein levels. Measuring the paraprotein levels and the paraprotein quantity difference between each sample is crucial in monitoring the disease progression. If the treatment is efficient, the paraprotein levels can be reduced (Haldeman-Englert et al., no date).

Serum protein electrophoresis (electrical separation) utilizes a liquid medium with wells and two electrodes, positive and negative, through which electricity runs. Since proteins are negatively charged, they move from the positive electrode to the negative one. As different proteins move at varying speeds through the gel medium, they are stained with a coloured dye, leaving marks along the gel medium. This separates different protein molecules in the solution, and any abnormal band of routine not present in the control plasma would indicate a pair of proteins (See figure 6). Therefore, serum protein electrophoresis provides an answer to the question of whether a paraprotein is present but not which type of M protein (Ahmad et al., 2023).

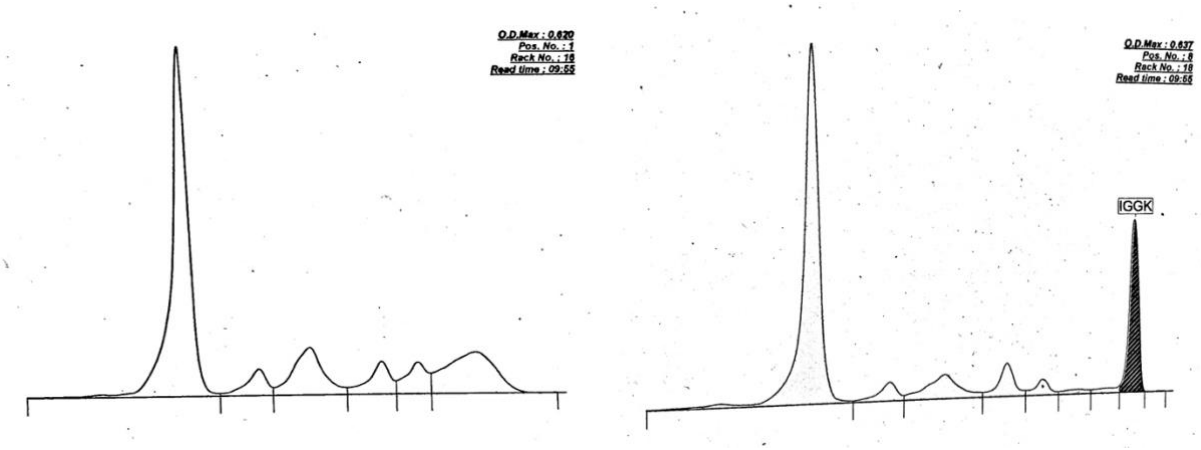


Figure 6: serum protein electrophoresis outcome of a normal result (left) and an abnormal result (right).

4.1.1.2 Immunotyping

After electrophoresis reveals the presence of a paraprotein, immunotyping can determine its specific type. This is a rapid and automated procedure. This technique relies on the principle of capillary electrophoresis in free solution. In this method, patient serum proteins are separated in silica capillaries based on their electrophoretic mobility and electroosmotic flow, under high voltage in an alkaline buffer. During migration, the proteins are directly detected by UV absorbance. During the analysis, immunoglobulins react with their respective antiserum. At the end, the ELP curve is overlaid on each antiserum. If the abnormality disappears in the antiserum-treated pattern, it confirms the presence of a specific monoclonal protein (See figure 7) (Sebia, 2021).

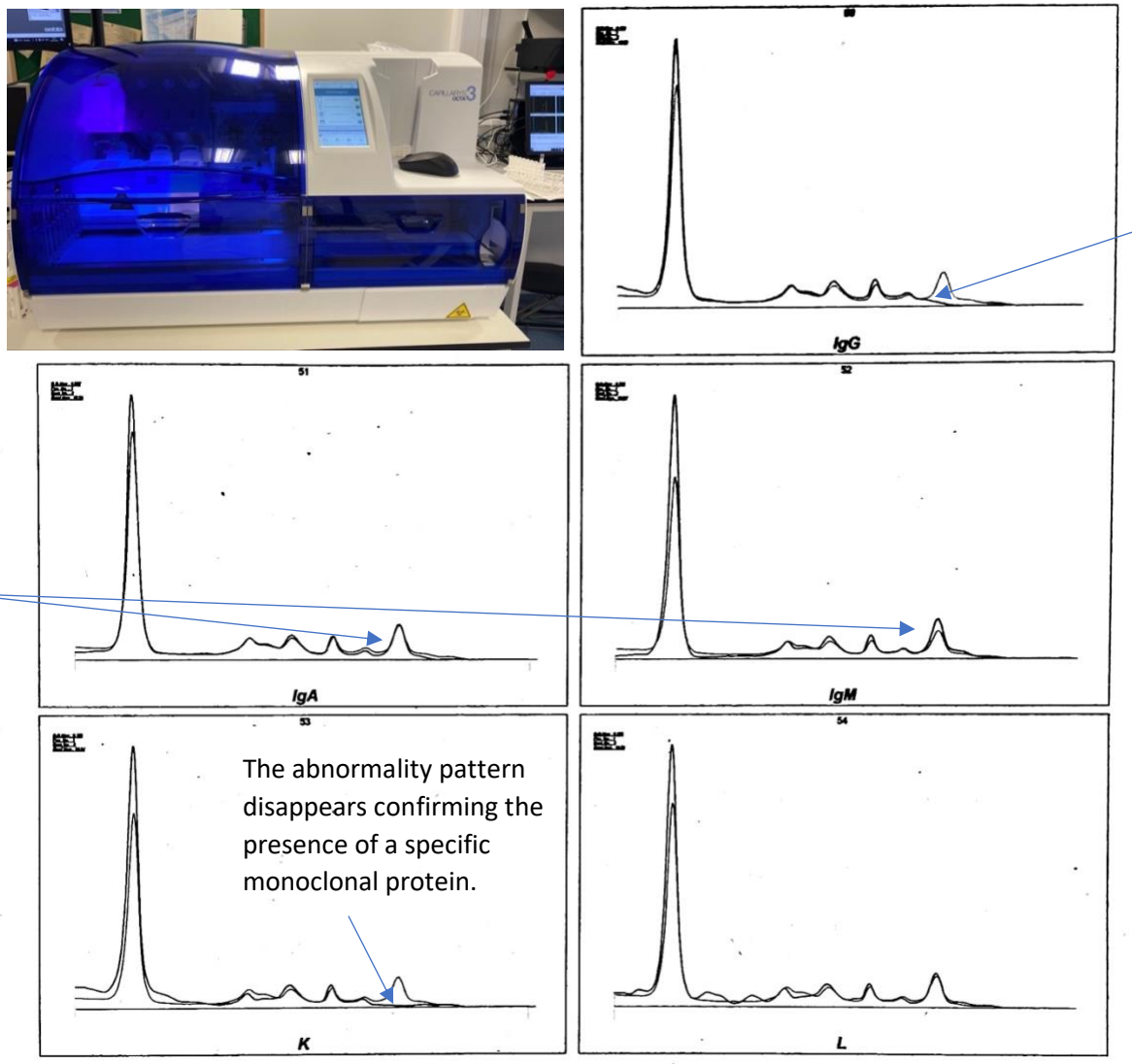


Figure 7: Sebia capillarys immunotyping equipment (left upper corner) and outcome. The patient presents IgG Kappa.

4.1.1.3 Immunofixation

Even though, the immunotyping can detect most of the monoclonal bands, sometimes it can be difficult to detect small bands using this technique. This is when the clinical staff perform the

immunofixation technique. In this test, the serum proteins are separated according to their charge and the gel is incubated with several specific antisera. These antibodies bind with the targeted immunoglobulin to form a complex, which provides a measurement of its concentration. This allows for the determination of the quantity of the heavy chain IgM or G and the light chains, lambda or kappa light chains (See figure 8) (Sebia, 2021).

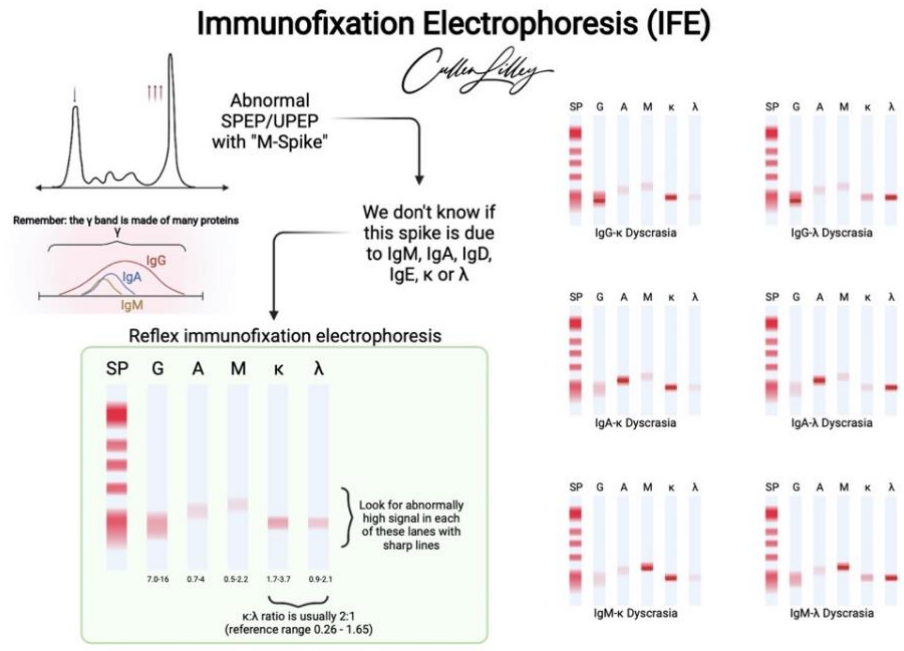


Figure 8: review of the immunofixation electrophoresis process (Lilley, 2021)

4.1.1.5 Other tests

- Total protein and albumin: B2 microglobulin and albumin facilitate the estimation of tumour burden and aids the prognostic scores. The higher the level of B2 microglobulin level, the worse the prognosis. On the contrary, the higher the albumin, the better the prognosis (Myeloma Uk, 2021).
- Calcium test: Performed to check if hypercalcaemia is present (Myeloma Uk, 2021).
- Serum Free light chain (SFLC): An abnormal ratio will pick up 98% of myeloma patients. Shows clonality established by the light chain restriction on immunophenotyping (Sive et al., 2021).

4.1.2 Urine based tests.

4.1.2.1 Urinary Bence-jones protein (BJP) assay/urine protein electrophoresis

Under normal circumstances, free light chains are filtered through the nephron and removed by the cells lining the tubules. However, in the case of myeloma, an excessive amount of free light chains can overwhelm the tubules' ability to remove them. This can result in blockages further along the nephron, preventing it from functioning correctly and ultimately causing significant kidney damage. These light chains are secreted into the urine and are identified with the Urine Bence jones assay. BJP is detected by urine protein electrophoresis (See figure 9) (Sive et al. 2021). This test operates in a similar manner as serum protein electrophoresis, but instead uses urine. It measures the concentration of light chains present in the urine, although it does not differentiate between the specific type of paraprotein that may be elevated.

Figure 9: urine protein electrophoresis and immunofixation equipment

4.1.2.2 Immunofixation

The procedure for immunofixation is the same for both urine and serum samples. Therefore, the monoclonal nature of the light chains present in the urine are confirmed (See figure 10).

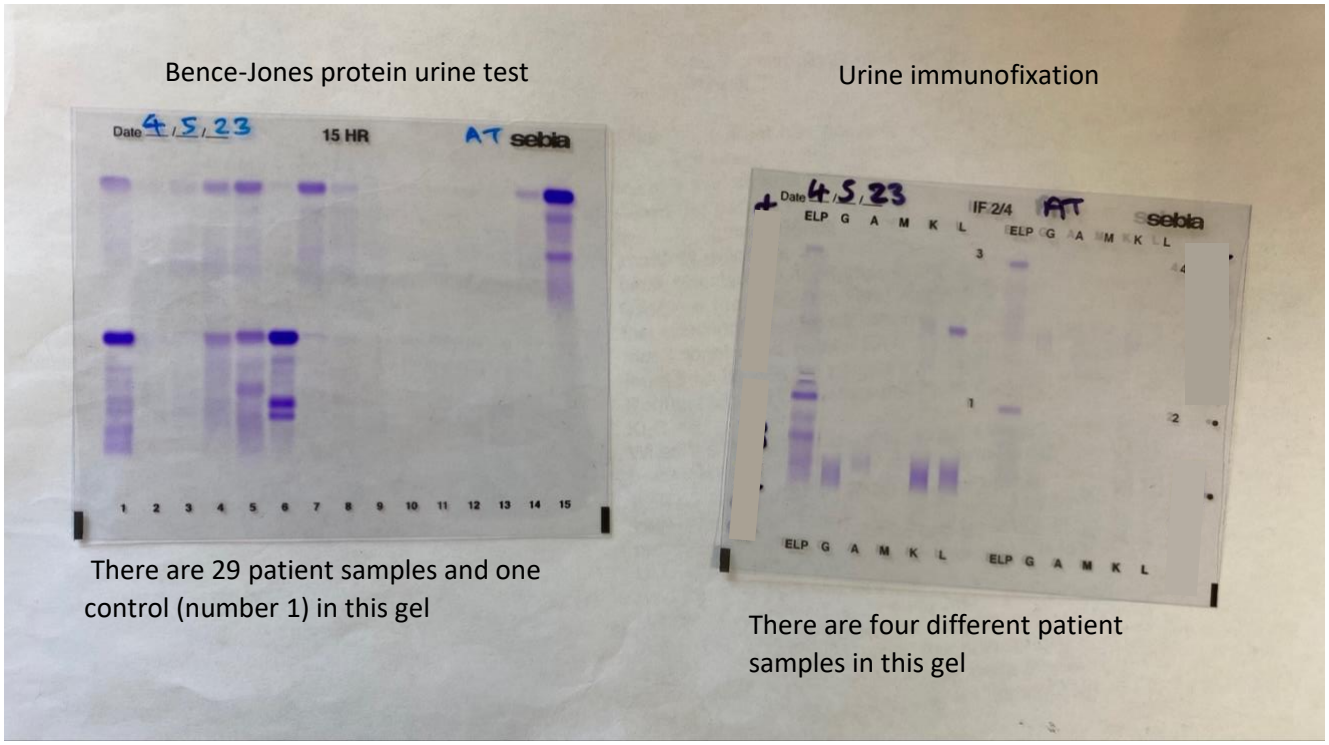


Figure 10: Gel outcomes when Bence-jones protein urine test and urine immunofixation are performed.

4.1.2.2 Urea and electrolyte profile (U&E)

This usually includes potassium, sodium, urea, creatinine and eGFR. It is done to check for renal pathologies. High creatinine and high uric acid (Myeloma UK, 2021).

4.2 Haematology tests

4.2.1 Bone marrow biopsy

To detect clonality and observe plasma cells (see figure 11), bone marrow aspirate and trephine biopsy are conducted by inserting a needle into the posterior pelvis to aspirate fluid, which contains a mixture of blood and bone marrow particles. The particles are then spread on glass slides, stained, and examined for plasma cells, which are represented as a percentage of total white cells. Further stains are used to identify and count plasma cells. Flow cytometry can also be used with a small portion of the aspirated material to confirm the percentage of plasma cells or detect other anomalies (Bain et al., 2019).

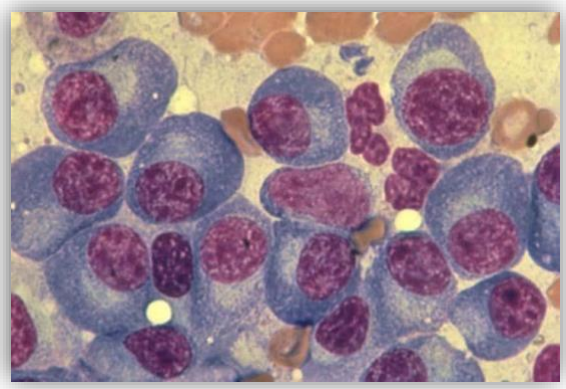


Figure 11: Bone marrow aspirate showing plasma cells (Dhaval Shah, 2002).

4.2.2 Full blood count (FBC)

This test can help identify anaemia in a patient, which may be caused by bone marrow being full. It can also indicate the presence of thrombocytopenia and leukopenia. Haemoglobin levels can decrease, and the thickness of the blood plasma may increase up to two years before a myeloma diagnosis. To confirm the presence of rouleaux (RBCs clumping together) caused by the viscosity of paraproteins bound to their surfaces, a blood film-peripheral smear is done (see figure 12). This clumping of RBCs leads to an increase in plasma viscosity. A plasma viscosity test may also be performed to evaluate the thickness of the plasma (Bates et al., 2017).

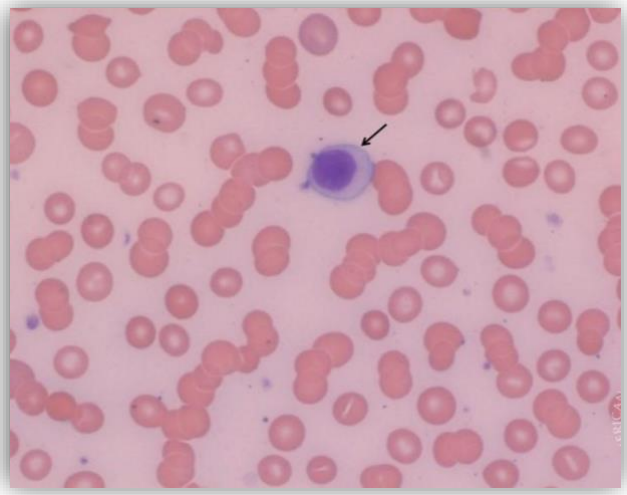


Figure 12: blood film-peripheral smear showing rouleaux and a plasma cell. (Heather Smith, 2018)

4.3 Imaging techniques

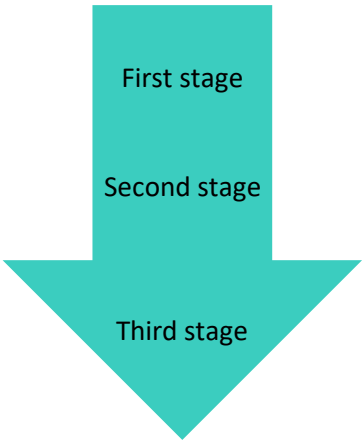
In addition, the patient can get imaging studies such as MRI or skeletal survey including an X-ray of the back and ribs to look for any lytic lesions. MRI is a more sensitive technique for detecting both bone lesions and bone marrow involvement by myeloma (See figure 13) (Myeloma UK, 2021).

Figure 13: a picture showing the multiple lytic lesions present in the bone (About cancer, no date).

As a conclusion, the criteria of diagnosis of multiple myeloma include plasma cells greater than 10% of bone marrow and evidence of end organ damage (CRAB) or specific biomarkers for cancer plasma cells greater than 60%, serum light chains greater than 100 mg/dl, and more than one focal lesions on MRI (Myeloma UK, 2021).

5. Staging of myeloma

Prognostic factors such as serum albumin, serum B2 microglobulin (SB2M), level of LDH, and genetic risk assessed by fluorescence in-situ hybridization (FISH), can be used to predict survival outcomes and are strong indicators of the stages of myeloma. The first stage represents the best prognosis and the third one the worst prognosis of the disease (*International Staging System for multiple myeloma,* 2014) (Rajkumar et al., 2014).

	SB2M < 3.5 mg/l; serum albumin > 3.5 g/dl; standard risk chromosomal abnormalities (CA) by fluorescence in-situ hybridization; and normal LDH.
	SB2M < 3.5 mg/l; serum albumin > 3.5 g/dl. Or SB2M 3.5 to 5.5 mg/L, regardless of the albumin
	SB2M > 5.5 mg/L and high-risk CA by FISH Or SB2M > 5.5 mg/L and high LDH

6. Treatment

While myeloma cannot be cured, treatment can keep the disease under control by reducing plasma cell levels and managing symptoms for as long as possible. The bone marrow microenvironment plays a crucial role in the growth, survival, and drug resistance of plasma cells in myeloma patients. This is why myeloma treatment focuses on the microenvironment as well as the tumour cells. The most used drugs to treat this condition are bortezomib, lenalidomide, thalidomide, and daratumomab. However, the treatment is tailored to meet the needs of each patient (Myeloma UK, 2018).

An autologous stem cell transplant (own cells) or an allogeneic stem cell transplant (donor to recipient) can increase the survival rates up to 6 years in most cases. This is why if the candidate is available for transplant, they then undergo the induction process to prepare them for the transplant. There are some factors that need to be taken into consideration to be transplant eligible such as the patient age (usually under 65 years old), no major underlying medical issues, and the type and stage of the disease (International Myeloma Foundation, 2021).

Treatment can relieve symptoms and minimize complications, improving the patient's quality of life and extending it. However, even with effective treatment, myeloma patients will experience relapses, the timing of which will depend on how well they respond to treatment and their individual circumstances. Since myeloma can vary from patient to patient, treatments may also differ.

6.1 Lines of treatment for myeloma

6.1.1 First line treatment

If candidate is available for transplant	If patient is not available for transplant
Induction options	**Treatment**
• Cyclophosphamide + bortezomib + dexamethasone (dex) • Bortezomib + lenalidomide + dex • Carfilzomib + cyclophosphamide + dex • Carfilzomib + lenalidomide + dex • Bortezomib + thalidomide + dex	• Cyclophosphamide + bortezomib + dexamethasone (dex) • Bortezomib + thalidomide + dex

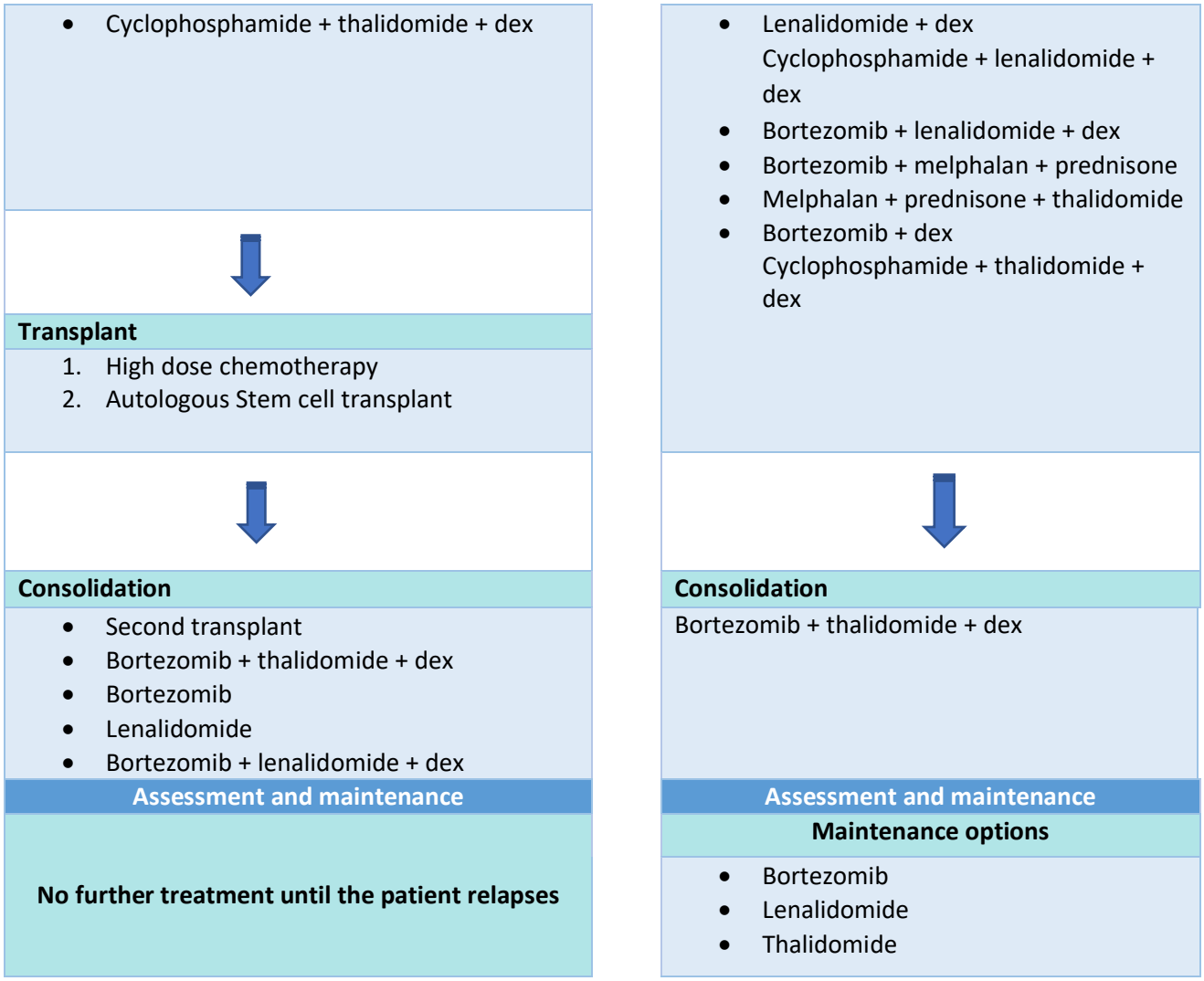


Figure 6: a diagram showing the different treatments available as a first line treatment (Myeloma New Zealand, 2020; Myeloma UK, 2018).

6.1.2 Second line of treatment (after first relapse)

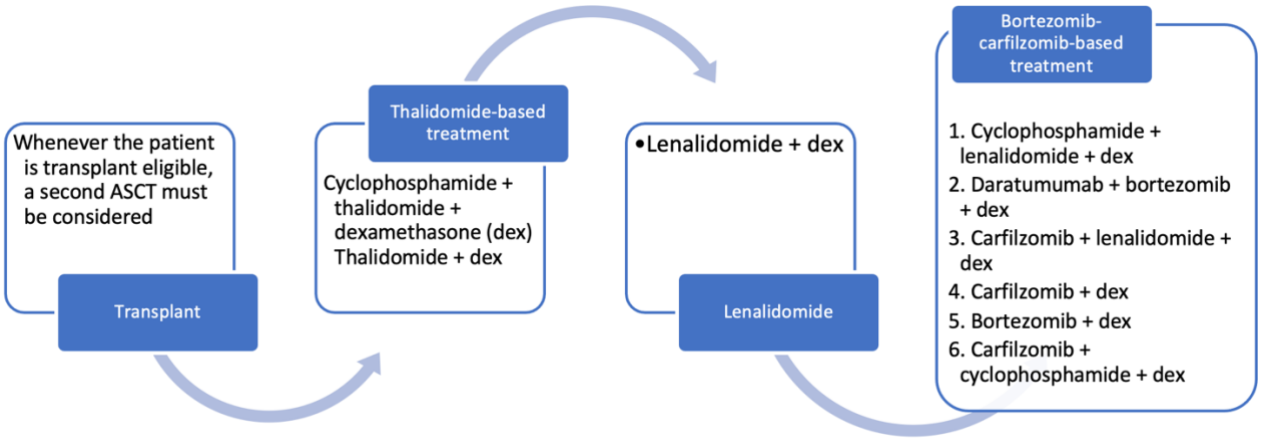


Figure 7: a diagram showing the different options given in the second line of treatment after the first relapse. The first option will always be a transplant. (Myeloma New Zealand, 2020; Myeloma UK, 2018).

6.1.3 Third line of treatment (second relapse)

The third line of treatment is given to patients who have their second relapse (Myeloma UK, 2018).

- Lenalidomide + dex
- Ixazomib, lenalidomide, and dexamethasone
- Panobinostat, bortezomib and dexamethasone

6.1.4 Fourth line of treatment (third relapse)

The fourth line is given to patients who have experienced their third relapse (Myeloma UK, 2018).

- Daratumumab
- Isatuximab, pomalidomide, and dexamethasone
- Ixazomib, lenalidomide, and dexamethasone
- Lenalidomide and dexamethasone
- Panobinostat, bortezomib and dexamethasone
- Pomalidomide and dexamethasone

5.1.5 Fifth line of treatment (fourth relapse and beyond)

The last line of treatment is in place for patients who have their fourth relapse and beyond (Myeloma UK, 2018).

- Lenalidomide and dexamethasone
- Panobinostat, bortezomib and dexamethasone
- Pomalidomide and dexamethasone
- DT-PACE
- Novel therapies

After the fifth line of treatment, myeloma is usually at a very advance stage and the treatment is focused on supportive care instead. This includes managing the symptoms to make sure the patient can keep the best quality of life possible (Myeloma UK, 2018).

6.2 Managing complications during treatment.

Managing myeloma complications include different matters to be taken into consideration (NICE, 2016) (Berenson, 2022).

- Renal failure can lead to dialysis. The doctor may also prescribe medications to control blood pressure and diuretics to help remove the excess of fluid (NICE, 2016) (Berenson, 2022).
- Anaemia: The bone marrow is damaged by myeloma and the production of blood cells can be lower causing anaemia. This can increase fatigue and shortness of breath. The development of anaemia will be monitored by FBC, and its management can require blood transfusions or erythropoietin-stimulating agents(NICE, 2016) (Berenson, 2022).

- Infection: antibiotics are commonly used to prevent infections caused by a weakened immune system. Myeloma treatment can make patients more susceptible to infections, that is why it is important to offer the patient the corresponding immunisation required(NICE, 2016) (Berenson, 2022).
- Bone disease: biphosphates prevent bone loss and prevent the risk of fracture. However, if any bones are at risk of fracture, surgical stabilisation followed by radiotherapy should be considered. In addition, dental assessment, and proper dental health care support should be offered to the patient. The doctor might prescribe pain relievers like nonsteroidal anti-inflammatory drugs (NSAIDs) (NICE, 2016) (Berenson, 2022).
- Spinal cord compression: surgery is needed to manage complications such as spinal cord compression (NICE, 2016) (Berenson, 2022).
- Supportive care: pain management and other symptoms such as fatigue and nausea (NICE, 2016) (Berenson, 2022).

7. Monitoring

A myeloma patient is monitored every 1 to 3 months to evaluate the response to treatment and check if the condition is being managed effectively. This detects any changes in the progression of the disease and the medical team can then make the appropriate adjustments to the treatment plan (Cancer Research UK, 2021) Risk factors such as impaired renal function, high-risk FISH and disease presentation are considered for progression. Monitoring for myeloma involves the assessment of myeloma-related symptoms from the treatment and the following laboratory tests (NICE, 2016):

- Serum protein electrophoresis (EPH)
- Urine protein electrophoresis
- Full blood count
- Bone profile
- Imaging tests for patients developing new bone symptoms.
- Bone marrow biopsy

8. Prognosis

DNA level modifications determine the behaviour of cancer cells. Chromosomal translocations occur early in the multiple myeloma and are seen in an approximate 50% of myeloma patients. This leads to an overexpression of partner genes, triggering abnormal clonal PC behaviour and different clinical outcomes. As an example, the translocation t(14,16) (part of chromosome 14 has swapped places with chromosome 16) is observed in less than five percent of myeloma patients and it is associated with poor survival. On the contrary, the t(11;14) is associated with favourable prognosis and it is present in approximately 20% of patients (Landgren & Morgan, 2014).

Myeloma is an uncurable condition; however, treatment can also enhance the survival rate (See figure 8) (Sive et al., 2021).

No treatment	→	8 months median survival
Chemotherapy	→	3 years median survival

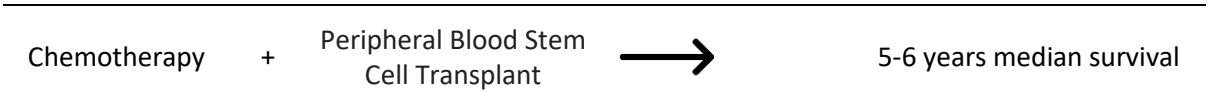


Figure 8: A diagram showing the prognostic according to the treatment chosen. These rates are variable considering the age of the patient (Sive et al., 2021).

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