What type of treatment will I have?

In recent years there have been huge developments in new treatments and a move away from traditional chemotherapy. It is now extremely likely that your consultant will discuss the current treatment approaches with a form of targeted, small molecule therapy.

Targeted therapies for treatment of CLL can be broadly considered as either 'Continuous' treatment or a time limited 'Fixed duration' treatment. These different regimes contain different drugs or combinations of drugs. Both these approaches work extremely well and there may not be a right or wrong choice in your case.

Your consultant will help by advising you of the way each of these approaches will differ. For example, side effects may be different and the effect of the drugs on your body will need monitoring in different ways.

Choosing a treatment approach takes several factors into account. Firstly, and most importantly, is your general health and what specific health issues you have, for example, heart problems or chronic kidney problems. Secondly, there may be biological characteristics of your CLL which influence the choice. Additionally, taking into account what is important to you - you may have a preference.

It is important that both you and your consultant are comfortable with the decisions you make together. Before you decide, it is always sensible to discuss with someone at home as well as with your clinical nurse specialist.

A clinical trial may be an option for you. Your consultant will be able to provide you with further information. Please see the section on Clinical Trials.

Treatments you may be offered include the following. The side effects and benefits of each treatment will be made as clear as possible by your medical team.

1. **Fixed duration therapy**

This is treatment which is given for a limited amount of time, and then stopped. You will still be closely monitored to make sure that your CLL does not return, and if this happens you may be restarted on the treatment.

Venetoclax with Obinutuzumab. This is used in first line treatment. Obinutuzumab is an antiCD20 antibody given as an intravenous infusion (also known as IV or 'drip'). The antibody sticks to the surface of the CLL cells, killing off much of the circulating cells. Obinutuzumab is given for several weeks before starting venetoclax tablets. Venetoclax is a BCL2 look-alike. BCL2 is a protein which triggers a process in the CLL cells causing them to die off rapidly. The obinutuzumab monthly infusions will be completed after 6 months but the venetoclax tablets continue throughout.

The whole course of treatment lasts just over 12 months.

Venetoclax and Ibrutinib: This is another 'frontline' regime. It combines oral Ibrutinib, a BTK inhibitor with venetoclax. It is an entirely oral regime and lasts approximately 15 months.

Commented [HL1]: Should we explain somewhere that continuous treatment is something you take until it ceases to be effective or the side effects prove too great. Do we need to explain relapse and remission? For both fixed duration and continuous treatment it may be necessary in due course to start a second line of treatment. It may be you have explained this elsewhere but I think it would be good for people to get a feel of how the longer term process might work.

Commented [bg2R1]: I've added a brief summary under each heading.

Commented [bg3]: Added to make clear.

Commented [bg4]: Capitals removed

Commented [NG5]: There is something missing here, perhaps that this is about how venetoclax works.

Commented [bg6R5]: Spotted. I've added in the missing piece.

Venetoclax and Rituximab: This can be given as a second (or more) line of treatment.

Rituximab is similar to obinutuzumab and is given intravenously. Venetoclax tablets start at the beginning of the regime and continue for 2 years. Once you are on the full dose of venetoclax you will start monthly doses of rituximab. After 6 doses of rituximab the venetoclax continues until the end of the 2-year course.

Traditional chemotherapy, usually known as **FCR** combines the chemotherapy tablets, fludarabine and cyclophosphamide with the antiCD20 monoclonal antibody, rituximab.

Because of side effects, this combination is much less used but for some people, particularly younger, fitter patients, has led to very long remissions.

Commented [HL7]: Maybe this should go under the fixed duration heading. I think it would be good to explain this is likely to be only prescribed for younger, fitter patients – the sort of wording you used before.

Commented [bg8R7]: Moved, and younger, fitter patients added.

2) Continuous therapy

This is treatment which continues until it stops becoming effective (relapses), or if side effects become too great. Different treatments may be considered if this occurs.

BTK inhibitor therapy: These are taken by mouth continuously and indefinitely. These drugs control CLL by isolating the cells from the vital chemical interactions which help sustain the CLL cells. By blocking a key intracellular pathway triggered by a receptor on the cell surface known as the B Cell Receptor, the CLL cells are unable to survive. This includes second generation drugs such as **acalabrutinib** and **zanubrutinib** as well as the longer established **ibrutinib**. These drugs can be given first line or later on after a venetoclax regime, for example.

Another B Cell Receptor pathway inhibitor, **idelalisib**, also taken by mouth as a continuous therapy, can be given for relapsed CLL. Idelalisib is usually combined with rituximab. It is used much less than BTK inhibitors but may have a role for some people.

CAR-T

Future therapies: There are new developments all the time which makes clinical trials very important in developing newer drugs and finding better combinations. BTKi, BCL2 type treatments, and monoclonal antibodies, will continue to be the cornerstone of frontline therapy in CLL for some time to come.

One area of research treating relapsed CLL is in the use of CAR-T cells. However, there are many challenges to this approach, and it is not yet established in CLL.