TREATMENT STRATEGIES FOR CHRONIC LYMPHOCYTIC LEUKEMIA

WITH DR. SUSAN O’BRIEN

CARE™ GLOBAL INTERVIEW SERIES
CARE™ GLOBAL INTERVIEW SERIES

ISSUE 01: TREATMENT STRATEGIES FOR CLL

There have been significant changes in the CLL treatment landscape with the approval of novel targeted therapies and greater understanding of how molecular and mutation status can guide treatment decisions. CARE™ Faculty recently spoke with CLL expert, Dr. Susan O’Brien to get a global perspective on these advances and how they have impacted her practice.

This is the first issue of a CARE™ Global Interview series and covers content on:

- The changing role of chemotherapy in front-line treatment
- Recent practice changing data in the front-line setting
- Considerations for treatment of relapsed/refractory CLL

DR. SUSAN M. O’BRIEN, MD
Chao Family Comprehensive Cancer Center;
Associate Director for Clinical Science,
Medical Director, Sue and Ralph Stern
Center for Cancer Clinical Trials and Research;
UC Irvine Health, University of California
What patient and disease characteristics do you consider when you are treating CLL?

I usually consider age, fitness, and also FISH status, IGHV, and TP53 mutations.

What is your treatment algorithm for patients in frontline CLL? Is there still a role for chemotherapy?

Really, the only place I would discuss chemotherapy as a frontline option is with fit, mutated patients, which represents only a minority of patients we see with CLL.

If I had a young, fit patient with a mutated IGHV gene then I would have a long discussion with them on using chemotherapy (specifically FCR) vs. targeted therapy. The reason I think there still is a role for chemotherapy in a small group of patients is that there are now three publications that have shown a plateau on the Progression Free Survival (PFS) curve in patients with CLL and a mutated IGHV gene receiving FCR. Looking at the MD Anderson data, which has the longest follow-up with FCR, at 15-16 years almost 50% of those people were still in remission, many of them with undetectable MRD.

Now does that mean a fraction of patients can’t be cured with targeted therapy in this rather favourable subset of patients? The bottom line is I don’t know because we need much longer follow up before we would even begin to see a plateau in the curve-if there was going to be one. With Ibrutinib, remissions are very durable, but because of the BTK mechanism of action MRD undetectability is quite uncommon. Recently venetoclax plus obinutuzumab was approved in the United States for frontline therapy. Although not yet approved in Canada, the potential advantage with the venetoclax-obinutuzumab combination upfront it is a finite duration therapy and a high degree of MRD negativity. However, given the short follow-up of that trial, and again the fact that we have 15-20 years of data with FCR that suggests a plateau, I will still discuss chemotherapy as an option for these patients.

If patients are fit but unmutated, I will generally not give them chemotherapy because we do not see the long-term plateau with FCR or any other chemotherapy regimen, so I will go straight to targeted therapy with ibrutinib.

If patients are older with a lot of comorbidities, they won’t be able to tolerate FCR anyway. In this case the patient’s mutation status is less relevant. PFS and toxicity of treatment are more important, so again I do not give chemotherapy in this setting.
What recent clinical data has had the most influence on the treatment landscape for CLL in the frontline setting?

The reason many people are moving away from chemotherapy in the frontline setting is because of the presentation of the ALLIANCE (also published in the NEJM) and ECOG 1912 trials at ASH last year.

On ALLIANCE:\(^2\):

- This was a 3-arm frontline trial in older patients investigating bendamustine-rituximab (BR) vs. ibrutinib (I) vs. ibrutinib-rituximab (I-R).
- The ibrutinib-rituximab and ibrutinib PFS curves were superimposable suggesting that the addition of rituximab for six cycles up-front had no long-term impact. (see figure 1)
- Results clearly showed a much longer PFS with ibrutinib (± rituximab) than with bendamustine-rituximab. It should be noted that bendamustine-rituximab is not a preferred regimen in some provinces in Canada (it is in the United States because of tolerability vs. FCR).

On ECOG 1912:\(^3\):

- This is a trial of FCR vs. ibrutinib-rituximab in younger, fit patients. The statements I make on this trial assume that I can substitute ibrutinib-rituximab for single agent ibrutinib (based on what we saw in the ALLIANCE trial).
- Interestingly ibrutinib showed longer PFS compared to chemotherapy in the overall population and had an overall survival advantage. Despite this finding, I stick to my original point about mutated patients. So far there is no difference in PFS seen in this patient population and more importantly, the follow-up is much too early to know if the advantage of ibrutinib-rituximab in mutated patients will be significant.

These trials were key because up until their presentation, the only randomized frontline trial we had was with ibrutinib vs chlorambucil. When it came to more effective chemotherapy as a comparator, there was no randomized data until six months ago at ASH. These data confirm the use of targeted therapy with unmutated patients.
What is your treatment algorithm for patients in relapsed/refractory CLL?

For relapsed/refractory patients I will generally not use chemotherapy because it is very clearly inferior to targeted therapy in this setting. The options for targeted therapy that we have at this point are ibrutinib if they did not get it up-front, or venetoclax-rituximab based on the MURANO trial.

• On Ibrutinib R/R Trials:
  • RESONATE\textsuperscript{4} compared ibrutinib vs. ofatumumab, showing ibrutinib significantly improves progression-free survival, overall survival, and response rate. It was this randomized trial that led to full approval of ibrutinib.
  • The 6 year follow up of RESONATE\textsuperscript{5} was presented at ASCO earlier this year and has been submitted for publication.
  • This showed sustained efficacy in pts with R/R CLL, including in patients with high-risk genomic features. Safety remained acceptable with no new safety signals over long-term therapy.

• On MURANO\textsuperscript{6}:
  • This randomized trial compared venetoclax-rituximab to bendamustine-rituximab in the relapsed setting. Results demonstrated significantly longer PFS with venetoclax. 63% of patients were MRD negative at the end of venetoclax-rituximab combination therapy. This was maintained in 48% of venetoclax-treated patients at 24 months.
  • Venetoclax is time limited and was given in this trial for 2 years before stopping therapy as opposed to staying on until progression or intolerance.

How do these approaches compare? One might think that you can look at the data from MURANO with the 6-year follow-up from RESONATE, but you can’t really do this. Along with all the other caveats and difficulties with comparing across trials, the median number of prior regimens in the MURANO trial population was 1 and the median number to prior regimens with patients that got ibrutinib in the RESONATE trial was 4. The obvious question then becomes whether there is any data breaking out patients who only had one prior regimen in RESONATE. With this you might get a better feel for how those regimens compare in a similar patient population. There is data that will be published showing that in patients treated with ibrutinib in RESONATE who have had only one prior regimen, the median PFS has not been reached and looks like it will be out along the lines of 4-5 years.

THE BOTTOM LINE IS WE HAVE TWO GREAT OPTIONS IN THE RELAPSE SETTING THAT ARE HARD TO COMPARE WITH NO HEAD-TO-HEAD DATA.
What else do you need to consider when managing patients on ibrutinib?

In general, ibrutinib is a very well tolerated drug. One of the ways to minimize early discontinuation is having a conversation with your patients about getting through some of the early, more annoying side effects that they have (such as diarrhea, mouth sores, etc.) that often are going to get better with time. These are not usually severe but what often happens is patients experiencing minor side effects know the long duration of treatment and think they will have to put up with it for years. This thinking makes them more likely to discontinue what would otherwise be a very effective drug. We have to really communicate and help patients understand that these side-effects are more than likely going to get better.

Two of the side effects that we have to worry a little more about are bleeding and atrial fibrillation. Bleeding is usually quite minor and typically ecchymosis. For most patients it is a very tolerable side effect. The side effect that causes most concern is when patients develop atrial fibrillation. The good news is that when you look at aggregate data it is only about 10-12% of patients and tends to be older men with pre-existing heart disease. Nevertheless, the concern is not just the fact that the patient develops atrial fibrillation but that ibrutinib impairs platelet function and then you are adding anticoagulation onto that. This can increase the risk of major bleeding.

Do I automatically take a patient off when they have atrial fibrillation? No. As with everything in life you have to weigh the risk-benefit. There might be patients I would take off ibrutinib if they are more frail and at greater risk of falling or if there are other side-effects that are making it hard for them to tolerate, knowing I could then switch over to venetoclax- rituximab. If a patient has just started on ibrutinib, is fit or doesn’t have high risk disease, and I expect that they are going to get many years out of it, then I am probably not going to stop them. With these patients, if they need anticoagulation, I leave it to the cardiologist and I will explain to them that they have to be a little more careful about bleeding. When considering the pool of data available to us, there are higher rates of bleeding (both minor and major) with ibrutinib but major bleeding is extremely uncommon.

A very important piece of information when patients develop a resistance to ibrutinib is to not take them off the drug immediately until you have an alternate plan set. We know that most patients who are progressing on ibrutinib do so very slowly, the most likely reason being that these patients have a mutation in BTK. The common mutations in BTK that often lead to resistance still allow ibrutinib to bind, but in a competitive, non-covalent fashion. Normally when ibrutinib binds, it is in a covalent fashion. It is not reversible so the only way the patients can have functioning BTK is to resynthesize it. While these patients may not have 24-hour coverage with ibrutinib there is probably still some binding and activity, making progression very slow.

What happens when patients start to show signs of progression on Ibrutinib?

A very important piece of information when patients develop a resistance to ibrutinib is to not take them off the drug immediately until you have an alternate plan set. We know that most patients who are progressing on ibrutinib do so very slowly, the most likely reason being that these patients have a mutation in BTK. The common mutations in BTK that often lead to resistance still allow ibrutinib to bind, but in a competitive, non-covalent fashion. Normally when ibrutinib binds, it is in a covalent fashion. It is not reversible so the only way the patients can have functioning BTK is to resynthesize it. While these patients may not have 24-hour coverage with ibrutinib there is probably still some binding and activity, making progression very slow.

What I typically do once resistance is determined is to switch to venetoclax or venetoclax-rituximab. It is very effective in this setting. There is a publication looking specifically at the outcomes of venetoclax in patients who were failing ibrutinib. The median number of prior regimens in that group was 4 and 45% of the patients had 17p deletion. This was a highly refractory group of patients who failed chemotherapy and failed ibrutinib. Not surprisingly given that setting, there was a high incidence of TP53 mutations. The overall response rate with single agent venetoclax was about 2/3rds and what was even more impressive is that those remissions were really durable. The median time to progression was about 2 years.

You have to weigh the risk-benefit of continuing treatment; something that should always be discussed with the patient.

My go-to strategy for patients who have developed ibrutinib resistance is to switch to venetoclax.
References


3. Shanafelt, et al. ASH 2018 Abstract #LBA-4


7. Jones JA et al. ASH 2014; Poster/Abstract 1990


Stay tuned for the next issue of the CARE™ CLL Global interview series with insights from Dr. Paolo Ghia Professor of Medical Oncology at the Università Vita-Salute San Raffaele in Milano – Italy!
ABOUT THE CARE™ FACULTY

The CARE™ (Community. Academic. Research. Education) Faculty is a Pan-Canadian group of leaders in their field who gather, discuss and address gaps in knowledge, to develop education initiatives that frame news from a Canadian perspective.

The vision of the CARE™ Faculty is to share opinions and update Canadian specialists with news and developments from key conferences framed in a Canadian perspective.

The mission of the CARE™ Faculty is to enhance medical education, with the explicit goal of improving patient outcomes.

Learn more at www.CAREeducation.ca