ADVANCES IN LLM

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Optimizing the Use of Oral Therapy in Lymphoma

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H&O Approximately what percentage of treatments for lymphoma are now administered orally?

JF Administration of oral therapy in lymphoma is a rapidly evolving area. Frequency of use depends on the disease subtype. In some diseases, such as chronic lymphocytic leukemia (CLL), oral therapy has nearly replaced intravenous chemotherapy for most patients. Randomized trials of patients with CLL have shown that oral regimens are superior to intravenous chemotherapy in several different outcomes. In contrast, oral therapy is less common in diffuse large B-cell lymphoma, where intravenous cytotoxic therapy remains standard. In my clinic, among patients with various types of lymphoma, I would estimate that up to a third are receiving oral therapies, rather than intravenous therapies.

The concept of oral therapy is often appealing to patients. Some patients believe that oral therapy will be safer or better tolerated than intravenous agents. However, there are toxicities associated with both types of treatments. Randomized trials comparing oral therapy to intravenous therapy show different side effect profiles, and it is difficult to say which is "better" for a given patient. For example, the RELEVANCE trial (Combined Rituximab and Lenalidomide Treatment for Untreated Patients With Follicular Lymphoma) compared intravenous chemotherapy to a regimen including oral lenalidomide (Revlimid, Celgene) in patients with indolent follicular lymphoma. The clinical outcomes were similar between the 2 arms, but the toxicity profiles were different. The rates of withdrawal based on adverse events were essentially the same in both arms. This finding suggests that toxicities still occur with oral therapy, and it is necessary to monitor patients receiving this type of treatment. We need to overcome the misconception that oral therapy automatically has a better toxicity profile.

> It can be challenging to assess whether the patient is adhering to an oral treatment regimen.

H&O What are the advantages and disadvantages of oral therapy?

JF There are several advantages to oral therapy. The lack of an infusion is appealing to patients. Administration requires much less time compared with intravenous treatment. Patients do not have to drive to a clinic. I practice in a rural area, where it is not uncommon for patients to

live 1 or 2 hours away. It is an investment of an entire day for these patients to visit the cancer center and receive intravenous treatment. The ability to take oral therapy at home is a timely advantage as we face the coronavirus. In many cases, clinicians are currently considering the use of oral therapy as a strategy to minimize patient interactions in infusion rooms.

There are several potential disadvantages for oral therapy compared with intravenous treatment. It is less easy to monitor patients who are receiving oral therapy. In contrast, when treatment consists of chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), I meet with patients before every infusion, and I can assess their status. Obviously, this approach is not feasible for a patient who is taking a pill daily at home. Therefore, an appropriate level of and strategy for monitoring patients receiving oral therapy must be built into the treatment course in an intentional way. It can be challenging to assess whether the patient is adhering to an oral treatment regimen. Another potential disadvantage is cost. Intravenous treatment and oral treatment can both be expensive. However, some insurance plans attach a disproportionate out-of-pocket expense to oral treatment as compared with intravenous treatment. (In our practice, we are almost always able to reduce this added expense.)

H&O Are there ways to measure adherence to oral therapy?

JF Adherence can be measured in various ways. One is by simply asking the patient about missed pills. I find that phrasing the question as "How many pills did you miss this month?" seems to give patients permission to admit to missing pills. Asking "Did you miss any pills?" can sound pejorative. Reconciliation involves asking the patient to bring the pill bottle to an appointment, and then counting the pills. Other, more sophisticated ways to measure adherence have been used, particularly in research studies. For example, there are pill bottles that can register the number of times they are opened.

H&O Is the rate of adherence to oral therapy known?

JF The literature is limited regarding adherence to oral therapy in lymphoma. The rate of adherence is not known. The contributing factors are not well-defined, and it is a complex area. That said, it is possible to extrapolate from other settings, such as chronic myelogenous leukemia or HIV, where the use of long-term oral therapy is more established. Low-grade toxicities that persist over a long period lead to decreased adherence. At the beginning of treatment, patients may be willing to experience side effects when their lymphoma is responding and scans show improvement. A grade 1 toxicity might be easy to tolerate for weeks or months, but not for years. I would speculate that low-grade adverse events decrease adherence, especially when the treatment is for a disease, such as indolent lymphoma, that is otherwise asymptomatic. Recurrence of indolent lymphoma does not cause any immediate symptoms.

H&O Is lack of adherence associated with poor outcomes?

JF The limited data appear to identify an association between lack of adherence and poor outcomes. Studies of ibrutinib (Imbruvica, Pharmacyclics/Janssen) show that outcomes are inferior among patients who discontinue treatment early or modify the prescribed regimen. For some oral drugs, the optimal duration of treatment is still not known. Studies are ongoing. There appears to be increasing enthusiasm for fixed-duration therapy rather than indefinite therapy. In the future, I speculate that we may see more opportunities to provide a drug holiday for selected patients on long-term oral therapy. Ultimately, use of sensitive techniques, such as assessment of minimal residual disease (MRD), may help us better understand when it is appropriate to stop some of these treatments, much like the situation in monitoring chronic myelogenous leukemia.

> It is helpful for a pharmacist or a specialized nurse to frequently review the patient's list of concomitant medications to identify any potential interactions.

H&O How can clinicians monitor patients receiving oral medications?

JF There are several evolving models. In our clinic, we have an embedded pharmacist. Every time we prescribe an oral medication, the pharmacist meets with the patient and reviews potential adverse events. The pharmacist becomes the primary contact, and follows up with the patient frequently by phone, before each refill. The pharmacist coordinates all of the patient's prescriptions.

Concomitant medications must be constantly managed. One example of a potentially dangerous situation would be if a patient receives an antibiotic to treat an infection while on oral therapy for lymphoma, as administration of certain antibiotics combined with certain oral lymphoma treatments can lead to adverse reactions. In other institutions, nurses play an increased role in the administration of oral therapy. Instead of an infusion nurse, there is an oral therapy nurse. Other institutions are experimenting with technologies such as phone apps that can help track adherence and adverse events.

H&O Are there any other notable drug interactions between lymphoma treatments and other common medications?

JF There are many. For example, cytochrome P450 (CYP3A4) inhibitors and Bruton tyrosine kinase inhibitors interact. Common CYP inhibitors include certain antihypertensive medications and proton pump inhibitors. It is helpful for a pharmacist or a specialized nurse to frequently review the patient's list of concomitant medications to identify any potential interactions.

H&O Does oral therapy in lymphoma pose any particular challenges?

JF The use of oral therapy in lymphoma represents a new paradigm. I was trained to prescribe intravenous chemotherapy, which involves a specific regimen given on a particular day. Patients are evaluated before each infusion. In contrast, oral therapy is administered in the patient's home, and it is necessary to develop an optimal treatment monitoring strategy. Experience is needed to optimize the treatment course, including the frequency of blood checks and in-person evaluations.

A particular challenge is posed by the prolonged nature of the treatment. In lymphoma, clinicians are familiar with prescribing a fixed number of cycles of treatment, such as 6 months of chemotherapy, to achieve remission. Many of the oral regimens are given continuously until relapse, often for years or even a decade or more. It can be challenging to reconcile the need to see patients for follow-up visits with the need to allow them to live their lives.

H&O Do you have any recommendations on how to optimize the use of oral therapy in lymphoma?

JF The main priority is to have a system in place, whether it involves a pharmacist, a nurse, or templates in the electronic medical record. The patient's management course should be tracked in a way that is as robust as the protocol for intravenous chemotherapy. It is also necessary to have an infrastructure that helps patients with reimbursements and arranges delivery of the medications from specialty pharmacies.

For the clinician, administration of oral therapy is not necessarily easier or less time-consuming than intravenous therapy. It is not equivalent to writing a prescription for antibiotics. The process is complicated, and involves obtaining approval, distributing the medicine, and tracking the outcomes. It is a different way to administer treatment; it is not necessarily easier or better.

That being said, many of the oral agents represent new classes of drugs that have improved outcomes and lengthened survival in many cases. We should not lose sight of the fact that this is an exciting time in the development of treatments for lymphoma, and that these oral medications are contributing to favorable changes in the natural history of these malignancies.

Disclosure

Dr Friedberg has received honoraria for DSMB participation from Bayer and Ascerta.

Suggested Readings

Casulo C, Friedberg JW. Chemotherapy free treatment of indolent lymphoma. *Hematol Oncol.* 2017;35(suppl 1):20-24.

Chen C, Kehtarnavaz N, Jafari R. A medication adherence monitoring system for pill bottles based on a wearable inertial sensor. *Conf Proc IEEE Eng Med Biol Soc.* 2014;2014:4983-4986.

Morschhauser F, Fowler NH, Feugier P, et al; RELEVANCE Trial Investigators. Rituximab plus lenalidomide in advanced untreated follicular lymphoma. *N Engl J Med.* 2018;379(10):934-947.

Williams AM, Baran AM, Casulo C, et al. Ibrutinib dose adherence and therapeutic efficacy in non-Hodgkin lymphoma: a single-center experience. *Clin Lymphoma Myeloma Leuk.* 2019;19(1):41-47.

Zackon AYL, Ayers AA, Yeager KA, et al. Maximizing the effectiveness of oral therapies in lymphoid cancers: research gaps and unmet needs. *Leuk Lymphoma.* 2019;60(10):2356-2364.