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Editorial Open Access

The Changing Therapeutic Landscape of Chronic Lymphocytic Leukemia

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Editorial

Chronic lymphocytic leukemia (CLL) is characterized by slow accumulation of mature but functionally incompetent lymphocytes which are monoclonal in origin. The disease course is highly variable--with some patients having long survival times and never requiring treatment and others who live only for a few years even with treatment.

In the past, the treatment of CLL consisted of chemo-immunotherapy, usually with FCR (fludarabine, cyclophosphamide and rituximab), PCR (pentostatin, cyclophosphamide, rituximab) or BR (bendamustine and rituximab). Not all patients with CLL will require treatment. Considering the adverse effects of traditional chemotherapy, only patients with disabling symptoms or cytopenias proven to be secondary to CLL (not autoimmune related) are usually treated. A high white cell count or disfiguring lymphadenopathy are not indications for treatment.

Recent developments in the understanding of the B cell receptor (BCR) and the B-cell receptor pathway signaling have changed the therapeutic landscape of CLL. Most promising of the small molecule inhibitors target the bruton tyrosine kinase (BTK), phosphoinositide 3 kinase (PI3K) and B cell CLL/lymphoma protein 2 (BCL-2) family proteins. Out of the novel agents, two of them have already been approved for the treatment of CLL.

Ibrutinib is a first-in-class oral, selective, irreversible inhibitor of BTK, a member of the Tec kinase family involved in the BCR signaling cascade [1]. The drug was approved by the Food and Drug Administration (FDA) on February, 2015 for the treatment of patients with CLL who received at least one prior therapy. The approval was based on an open label multi-center study conducted by Byrd et al. [2]. They demonstrated an overall response rate of 58.3% in 48 patients with CLL who were treated with 420 mg of ibrutinib daily. The patient population was heavily pretreated (median number of previous therapies was 4) and the responses were independent of high risk features including 17p deletion. Toxic effects were limited, and responses were often durable with prolonged therapy. This benefit was later confirmed in a randomized open label multi-center phase III trial of ibrutinib versus ofatumumab in 391 previously treated patients with CLL or small lymhocytic lymphoma (SLL) [3]. The ORR, OS and PFS were significantly higher in the ibrutinib arm. Treatment with Ibrutinib is associated with an initial lymphocytosis which does not signify disease progression but rather the migration of leukemic B cells from the lymph nodes, bone marrow and spleen into the blood.

Idelalisib is a potent, oral, selective inhibitor of PI3Kdelta and promotes apoptosis [4]. FDA granted accelerated approval to idelalisib in July 2014 for treatment of relapsed follicular lymphoma or CLL/SLL who have received at least 2 prior lines of therapy. This was based on a phase II open label; multi-center trial of 125 non-Hodgkin lymphoma patients [5] 25 patients had SLL. Again, the patient population was heavily pretreated. The ORR was 57% with majority of them being PRs and the median duration of response was 12.5 months. Toxicity was higher than with ibrutinib with febrile neutropenia, diarrhea, colitis and pneumonia being the most common serious adverse effects. Transient lymphocytosis due to migration of lymphocytes was also seen with idelalisib. Another phase III randomized, double blind study of idelalisib with rituximab versus placebo with rituximab in patients with heavily pretreated relapsed/refractory CLL showed significantly improved ORRs (81% versus 13%; $p<0.001$) and the OS rates at 12 months were 92% versus 80% ($p=0.02$) [6]. The responses were independent of high risk features and toxicities were slightly higher in the idelalisib group. Considering the results of this study, a combination of idelalisib and rituximab was recently approved for relapsed CLL.

These drugs raise some important points. The efficacy and the relatively low adverse effect profile of these drugs will have an impact on in the upfront setting in the treatment of CLL. In some patients with indolent disease, these drugs may completely replace traditional chemotherapy. As the responses are independent of high risk features, current prognostic markers may need to be reexamined. Since complete remissions are less common with these targeted therapies, the implication is that this will be a long term treatment much like the TKIs for CML. The typical scenario is that of an elderly patient in his 70's who needs therapy and will take an oral drug and manage his CLL for the rest of his life. This also raises issues about compliance as well as financial aspects of the therapy. We may also start seeing a trend to treat patients in earlier stages of their disease due to their ease of administration and low toxicity profile. Lastly, with more novel agents in development, prioritizing the different lines of therapy warrants a discussion as well.

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