Editorial

Hope for high risk chronic lymphocytic leukemia after ibrutinib failure

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Chronic lymphocytic leukemia (CLL) is characterized by progressive accumulation of mature appearing, dysfunctional CD5 positive B lymphocytes. The prognosis of the disease is extremely variable and ranges from patients free of symptoms, having almost normal life span, to an aggressive course of disease which is unresponsive to therapy and often leads to short survival. Prognostic factors including clinical, genetic, molecular and biochemical characteristics can help to identify patients with an expected unfavorable course of disease. Two main subsets of CLL, which differ in clinical behavior, can be distinguished by whether or not CLL cells express an unmutated or mutated gene of immunoglobulin heavy chain variable region (IGHV), reflecting the stage of normal B cell differentiation from which they originate (1). Chromosomal alterations are present in most CLL patients and affect prognosis. CLL with del13q, including deleted region of miR-15a/16-1, which regulates the expression of anti-apoptotic BCL-2 protein is associated with favorable prognosis. At the other end of the spectrum, CLL with del 17p is associated with loss of the tumor suppressor gene TP53, which confers poor prognosis with chemoimmunotherapy (2).

Survival of CLL is dependent on functional B cell receptor (BCR) signaling. The advance of kinase inhibitors, which block BCR signaling, highlighted the potential of targeted therapies in CLL and led to a paradigm change in therapy (3). Specifically, the development of Bruton tyrosine kinase (BTK) inhibitors, such as ibrutinib, has made major advances in CLL therapy, particularly in patients who are unfit for chemoimmunotherapy as well as patients with high risk features such as del17p and TP53 mutations, and patients with relapsed disease or those who are refractory to fludarabine therapy (4-6).

CLL progression and transformation on ibrutinib therapy

Although ibrutinib produces durable remissions in the majority of patients, some patients do experience relapse with progressive CLL or Richter's transformation. The longest experience with ibrutinib in relapsed or refractory (R/R) disease resulted in 5-year progression free survival (PFS) and overall survival rate (OS) of 36% and 60% respectively (7). Patients with adverse prognostic factors, in particular patients having both complex karyotype and del17p, experienced shorter PFS and OS of 25 months and 32 months. Richter's transformation tends to occur within the first two years of ibrutinib therapy, and remain stable for 10% of patients at the four year follow up (8). The molecular mechanisms leading to transformation are not yet understood. Disease progression on ibrutinib primarily occurs due to acquired mutations in BTK, or its downstream target PLCγ2. Functional studies have shown that C481S mutation in BTK confers resistance to ibrutinib by preventing irreversible drug binding (9). Gain of function mutation in PLCγ2 allows BCR mediated activation that is independent of BTK (10). High sensitivity assays show that mutations in BTK or PLCγ2 are present in 85% to 90% of CLL patients on ibrutinib at time of relapse (9). Other resistance mechanisms include development of

resistant clones and subclones which were already present before ibrutinib treatment (11). Clonal evolution, with the selection and expansion of clones containing del8p, results in TRAIL insensitivity through haploinsufficiency of TRAIL receptor (11). Although many patients can achieve excellent disease control on ibrutinib, the presence of poor risk factors, particularly del17p or TP53 mutations and complex karyotypes, often leads to the development of resistance mutations, and subsequently to disease relapse, even after an initial response to therapy. In a few patients, CLL progression occurred within the first year of treatment with ibrutinib, however the rate of CLL progression on ibrutinib increased significantly over time.

Ibrutinib treatment discontinuation

Ibrutinib is rarely discontinued for CLL progression during the first year; on average, 5% of patients were discontinued at 2 years, 10% at 3 years, and 20% at 4 years (8). The median survival of relapsed CLL patients on ibrutinib ranges from 3 to 23 months (8,12,13). These poor outcomes clearly show that ibrutinib refractory patients are an especially high-risk population. Discontinuation and dose reduction due to adverse events occurs more frequently during the first year, and tends to decrease over time.

In addition to better response and survival of high-risk characteristics, ibrutinib is not myelosuppressive, and its safety profile over time remains acceptable and manageable. Nevertheless, more than half of patients (52%) discontinue therapy within 4 years (7). Treatment discontinuation is equally attributed to either adverse events or disease progression and transformation (13,14). Even minor adverse events have significant effect on quality of life, as well as compliance, when treatment is taken on an ongoing basis. Infections, cytopenia, diarrhea, hypertention, atrial fibrillation and bleeding are among the notable adverse events. Although ibrutinib is considered to be less immunosuppressive than conventional chemoimmunotherapy, invasive fungal infections, in particular invasive aspergillosis with cerebral involvement, were reported (15).

Venetoclax first BCL-2 antagonist

Venetoclax is a BH3 mimetic that targets and selectively inhibits the anti-apoptotic BCL-2 protein. It has high binding affinity for BCL-2 inducing apoptosis independent of the BCR pathway. The overall response rate (ORR) of venetoclax in early studies was 79% in all subgroups and did not vary markedly among subgroups, including fludarabine resistant patients (16). A pivotal phase 2, open-label, multicenter study evaluated the activity and safety of venetoclax in 107 patients with refractory or relapsed CLL harboring del17p. The ORR was 79% with complete remission (CR) occurring in 8% of patients (17). Based upon that evidence, the FDA approved venetoclax for patients with del17p who had prior therapy. Importantly, response rates were high even in patients failing chemoimmunotherapy, and CLL with bulky lymphadenopathy. Venetoclax is particularly attractive for CLL as it is able to produce a deep response with undetectable minimal residual disease (MRD), and overcomes the disadvantage of BCR inhibitors which rarely produces MRD negative response. More than a third of patients who achieved CR with venetoclax had MRD negative CLL in bone marrow (16). Depth of response increased with length of therapy, and patients who achieved MRD negativity in peripheral blood had a longer estimated PFS compared with MRD-positive patients (18). Sixty-two percent of patients with R/R CLL treated with a combination of venetoclax and rituximab achieved clearance of MRD, and maintained it over time (19). Thirteen patients discontinued venetoclax after achieving an MRD negative response, and were still in remission nine months later. Given these deep and durable responses, even an abbreviated course of therapy with venetoclax may be sufficient, an advantage over BCR inhibitors.

Venetoclax in relapse refractory CLL failing ibrutinib

The efficacy of venetoclax in patients with CLL who had previously failed BCR inhibitors was reported by Jones et al in a multicenter, open label, non-randomized, phase 2 trial (20). An interim analysis reported on 91 patients with R/R CLL who had previously received ibrutinib as their last BCR inhibitor before enrolment. Most patients discontinued ibrutinib therapy due to CLL progression (55%) or adverse events (33%). Those who discontinued due to adverse events subsequently suffered disease progression. At median follow up of 14 months (8–18 months) the ORR to venetoclax was 65% (95% CI, 53–74%) with 56% partial response (PR) or nodular PR, 9% CR or CR with incomplete marrow recovery, and only in 5% with disease progression. Responses were observed also in patients with poor risk factors including high-risk

chromosomal abnormalities. MRD assessed from peripheral blood in 57 patients at 24 weeks post treatment initiation was negative in 24 (42%). Duration of response correlated with MRD status: 27.4 months median PFS (15.4–not reached) in MRD positive, and not reached in (95% CI, 19.2–not reached) in MRD negative disease. The median OS was not reached (27.8–not reached), estimated OS at 12 months was 91% (83–95%). Out of 17 patients who tested positive for BTK or PLCγ2 mutations, 71% responded to venetoclax. Serial data of decrease in allelic frequency of C481S mutation suggest that venetoclax may eradicate ibrutinib resistant clones. Despite concerns of tumor lysis syndrome (TLS), no clinical TLS observed, and only two patients experienced laboratory TLS, despite high tumor burden. Thirty five percent of patients interrupted venetoclax treatment, primarily because of disease progression (24%), Richter's transformation (5%) and adverse events (7%). The treatment was tolerable and no treatment related deaths were reported, however, six deaths occurred within 30 days after the last dose of Venetoclax. The contribution of venetoclax to the toxicity needs to be clarified on a case by case basis, and requires large scale studies.

In conclusion, the development of novel oral targeted therapies including BTK inhibitors and a BCL-2 inhibitor dramatically altered the therapeutic landscape of CLL. BTK inhibitors led to major improvements in outcomes, particularly for patients with R/R CLL, and those with TP53 aberrations. Although sustained disease control can be achieved with ibrutinib, patients with high risk prognostic factors often relapse and some develop resistance mutations. Patients who are refectory or relapse after ibrutinib have poor outcome. In addition, a major downside to ibrutinib therapy is that it does not achieve MRD-negative CR, and therefore in the majority of patients, it is given for a prolonged period of time. Cumulative risk of toxicity due to continuous therapy increases the rate of treatment discontinuation. Venetoclax is highly active in patients with R/R CLL previously treated with ibrutinib. Treatment with venetoclax has the potential to produce deep responses and MRD negativity with fixed duration therapy, as opposed to continuous therapy. The rapidly evolving novel therapies in CLL aim to increase efficacy, decrease toxicity and achieve MRD negative complete response, and hold the potential for short term chemo free targeted therapy.

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