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Drug Review: Ibrutinib

Abstract

Ibrutinib is an irreversible BTK inhibitor, characterized by high selectivity and potency. It has revolutionized the therapy of B-cell lymphomas, especially chronic lymphocytic leukemia (CLL) and mantle cell lymphoma. Importantly, it has expanded the armamentarium for those patients who are refractory to conventional chemoimmunotherapy. This small-molecule inhibitor has shown efficacy in this difficult-to-treat subset – those with del(17p)/TP53-mutated CLL. Its immunomodulatory properties make it an excellent choice for combining with other immunotherapeutic agents such as venetoclax. The drug is not without drawbacks. The need for indefinite therapy and the presence of adverse effects such as infection, bleeding, hypertension, and arrhythmia temper our enthusiasm for this versatile drug. But overall, ibrutinib's favorable risk profile and lack of myelosuppression make it an ideal therapy for the elderly and those with multiple comorbidities.

Keywords: *Bruton tyrosine kinase inhibitors, chronic lymphocytic leukemia, ibrutinib*

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Introduction

Chemoimmunotherapy has been the standard of care for chronic lymphocytic leukemia (CLL). However, its limitations are becoming increasingly apparent in the current era. The extensive study of tumorigenesis and other aspects of cancer cells has led to the identification of various targets for therapy. One such targeted drug is the small-molecule inhibitor ibrutinib, which has led to a paradigm shift in the treatment approach to indolent lymphomas.

Mechanism of Action

Bruton tyrosine kinase (BTK) is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine pathway. It is expressed on B lymphocytes, myeloid cells, and platelets, but is undetectable on T lymphocytes and plasma cells. BTK acts by transmitting and amplifying signals from the cell surface. The activated BTK triggers downstream signaling cascades including (PI3K)–AKT, PLC, PKC, and NF-κB. This results in B-cell survival, proliferation, and differentiation.[1]

The activation of B-cell receptor signaling in secondary lymphatic organs is the driver behind malignant cell proliferation. It is implicated in the pathogenesis of mantle cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, and CLL. Notably, CLL cells have a significantly higher level of BTK phosphorylation in comparison to normal B-cells.[2] Ibrutinib exerts its action via multiple pathways including:

1. It forms a covalent bond with a cysteine residue (Cys-481) in the BTK active site, leading to sustained inhibition of BTK enzymatic activity. Through BTK inhibition, downstream signal transduction pathways (MAPK, PI3K, and NF-κB) are also inhibited[3]
2. It alters the immune microenvironment and disrupts signals that help in CLL cell survival and migration[4]
3. It inhibits interleukin-2-inducible T cell kinase – this drives CD4 cells toward a TH1 phenotype enhancing tumor surveillance[2]
4. It reduces T-cell activation and proliferation and the resultant pseudo exhaustion seen in CLL.[2]

BTK also affects cell motility and homing. This explains the redistribution of lymphocytes from the lymph node into the peripheral blood seen with ibrutinib therapy. This distinct response of rapid shrinkage of lymph nodes and transient lymphocytosis is termed as "redistribution lymphocytosis."

The redistributed cancer cells are deprived of survival signals and eventually die. The

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median time to resolution of this effect is 14 weeks. This class effect is also seen with other BTK, SYK, and PI3K inhibitors. This novel response led to the coining of a new response criteria terminology – partial response with lymphocytosis.[5]

Food and Drug Administration-Approved Indications

The US Food and Drug Administration (FDA) approved ibrutinib in 2013, and the Indian Central Drugs Standard Control Organization (CDSCO) approved it in 2015.

1. MCL: Who have received at least one prior therapy*
2. CLL/small lymphocytic lymphoma with/without 17p deletion*
3. Waldenström's macroglobulinemia (WM)
4. Marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based therapy
5. Chronic graft-versus-host disease (GVHD) after the failure of ≥1 line of systemic therapy (*indications approved by the CDSCO).

The FDA-approved orphan designations include DLBCL, follicular lymphoma, multiple myeloma, pancreatic carcinoma, and gastroesophageal junction adenocarcinoma.[6]

Pharmacology

The drug is rapidly absorbed after oral administration, and the maximum plasma concentration is reached in 1–2 h. Its oral bioavailability is only 2.9% in fasting state but is doubled when taken with food. There is complete occupancy of the BTK site for 24 h after oral administration. The half-life of the drug is 4–13 h and excretion is 80% via feces and <10% by urine.[7]

Table 1: Dose modification[7]

Special populations	Dose modification
Elderly (age ≥65 years)	No dose modification
Pediatric population	No data
Renal impairment	Creatinine clearance ≤30 ml/min - use only if benefits outweigh risks
	Severe renal impairment/dialysis - no data
Hepatic impairment	Child-Pugh class A - 280 mg daily
	Child-Pugh class B - 140 mg daily
	Child-Pugh class C - contraindicated
Severe cardiac disease	Excluded from clinical studies

Posology of Ibrutinib

- CLL and WM: 420 mg once daily (three capsules of 140 mg)
- MCL, MZL, and GVHD: 560 mg once daily (four capsules of 140 mg).

It is administered once daily in a fasting state (30 min before or 2 h after a meal). Treatment is continued indefinitely till disease progression or intolerance.[6,7] Dose modifications for special populations are shown in Table 1.

Drug Interactions

Ibrutinib is predominantly metabolized by the CYP3A4 enzyme system. Hence, ibrutinib has interactions with some commonly used drugs [Table 2].

Adverse Effects

Ibrutinib's side effect profile varies significantly from the conventional regimens for CLL [Table 3]. Available evidence suggests that adverse effects are more common in the elderly population.[8]

Indications for interrupting therapy include new-onset or worsening grade ≥3 nonhematological toxicity, grade ≥3 neutropenia with infection/fever, and Grade 4 hematological toxicities. It is reinitiated at the starting dose once toxicity resolves. The dose is reduced by one capsule if toxicity recurs and a second reduction may be considered as needed. If toxicity recurs following two dose reductions, ibrutinib should be permanently discontinued.[6]

Infection

Despite not being myelosuppressive, ibrutinib is associated with a higher risk of infection. The highest risk of infection is in the first 6 months of therapy.[9] The risk decreases with time. Humoral and cell-mediated immunity improves with continued therapy.[10] The incidence of infection is higher when ibrutinib is used in the relapsed setting when compared to the upfront setting. This suggests that the underlying disease also plays a role.[11]

The decrease in macrophage activity, inhibition of interleukin (IL)-2-inducible T-cell kinase, and inhibition of NK cell-mediated ADCC are the mechanisms through which ibrutinib predisposes to infection. The decreased phagocytic activity by macrophages leads to

Table 2: Potential drug interactions[6,7]

	Drug	Recommendation
Strong CYP3A4 inhibitor	Itraconazole, voriconazole, posaconazole, indinavir, nelfinavir, ritonavir, saquinavir, and clarithromycin	Avoid the inhibitor or reduce the dose of ibrutinib to 140 mg capsule
Moderate CYP3A4 inhibitor	Fluconazole, erythromycin, aprepitant, atazanavir, ciprofloxacin, diltiazem, verapamil, and amiodarone	Reduce the dose of ibrutinib to 280 mg
Mild CYP3A4 inhibitor	Azithromycin, fluvoxamine	No dose adjustment
Strong CYP3A4 inducer	Rifampicin, carbamezapine, phenytoin	Avoid the inducer drug or closely observe for lack of efficacy

Table 3: Reported adverse effects[7]

	Very common	Common	Uncommon
Infections	Pneumonia, URTI, skin infection	UTI, sinusitis	Cryptococcal infection, pneumocystis infection, *Aspergillus* infection, hepatitis B reactivation
Neoplasm		Nonmelanoma skin cancer	
Hematological	Neutropenia, thrombocytopenia	Febrile neutropenia	Leukostasis
Immune system disorders		Interstitial lung disease	
Nervous system disorders	Headache	Peripheral neuropathy	CVA, TIA
Cardiac	Hypertension	AF	Ventricular tachy-arrythmias
Bleeding	Bruising	Epistaxis, petechiae	Subdural hematoma
Gastrointestinal	Diarrhea, vomiting, stomatitis		
Musculoskeletal	Arthralgia		
General	Peripheral edema, fever		
Skin	Rash		

URTI – Upper respiratory tract infections; UTI – Urinary tract infection; TIA – Transient ischemic attack; AF – Atrial fibrillation; CVA – Cerebro vascular accident

a susceptibility to *Aspergillus* infection. Predominant sites of involvement by aspergillosis are central nervous system and lungs.[12] Ibrutinib has also been shown to predispose to *Mycobacterium tuberculosis*, which is relevant in developing countries with a higher infection burden.[13]

Recommendation

1. Varicella-zoster prophylaxis is recommended only in the setting of relapsed CLL
2. No prophylaxis recommended for bacterial infections
3. Vaccination for influenza and *Pneumococcus* prior to starting ibrutinib
4. To maintain a high index of suspicion for aspergillosis, especially if there are risk factors such as concurrent steroids, diabetes, liver disease, and a number of prior cancer therapies.[14,15]

Bleeding

Ibrutinib is associated with a nearly three times higher risk of bleeding.[16] Among those treated with ibrutinib, 6% will experience major bleeding including gastrointestinal bleed, intracranial bleed, and hematuria, while up to 66% will experience minor bleeding such as contusion, epistaxis, and petechiae. Although thrombocytopenia contributes to bleeding, it is the interference with platelet aggregation due to both on-target and off-target kinase inhibition that is the main cause of bleeding.[17]

The use of ibrutinib with warfarin is contraindicated due to reports of incidental detected subdural hematoma in initial trials.[18] The newer oral anticoagulant – apixaban – has significant drug interaction with ibrutinib but is considered relatively safe to use.[19,20]

Recommendation

1. If an invasive procedure is planned – withhold ibrutinib for 3–7 days before and after the procedure
2. If the patient requires anticoagulation – low-molecular-weight heparin is preferred provided that platelet count is >50,000/μL
3. If the patient requires dual-antiplatelet drugs – consider ibrutinib along with 81-mg aspirin
4. Minor bruising on ibrutinib – no need to withhold ibrutinib
5. Clinically relevant bleeding while on ibrutinib – withhold ibrutinib. Transfuse platelet even in the absence of thrombocytopenia. Platelet transfusion is more effective after the effect of ibrutinib wears off. Hence, a repeat platelet transfusion is advised again after 3 h
6. Avoid concomitant intake of supplements such as fish oil and Vitamin E.[7]

Diarrhea

It is another common side effect of ibrutinib with a reported incidence of 50%. It is more common in the initial 6 months and is attributed to off-target action on epidermal growth factor receptor (EGFR). Diarrhea is short lived (6–20 days) and usually Grade-1.[14]

Recommendations

1. For Grade 1 diarrhea – continue ibrutinib
2. In case of high-grade diarrhea – temporary interruption of ibrutinib and the use of loperamide is recommended. A short course of steroids may be tried if infective diarrhea is ruled out.

Atrial Fibrillation

Patients on ibrutinib are associated with a 4%–10% higher risk of atrial fibrillation (AF) when compared to the general population, and it constitutes the major cause of ibrutinib discontinuation.[21] Like other adverse effects – AF is seen more often during the initial months of ibrutinib with no reports of AF after 18 months of

therapy. It is attributed to the regulation of PI3K-AKT, which regulates cardiac protection during stress. Ibrutinib causes an increase in late sodium current and enhanced automaticity of the cardiomyocytes – thus predisposing to AF.[22]

Recommendation

1. Prior AF or cardiac arrhythmia is not a contraindication for ibrutinib
2. Preexisting AF with a high risk of stroke (CHA2DS2-Vasc score >2) – anticoagulation is mandatory, hence ibrutinib is contraindicated
3. If the patient develops an unprovoked, initial AF or ventricular tachycardia in the first 3 months of ibrutinib therapy – further ibrutinib use is contraindicated
4. Ibrutinib has significant interaction with several anti-arrhythmic agents including diltiazem, verapamil, amiodarone, and digoxin. Beta-blockers such as metoprolol are preferred for the management of preexisting tachyarrhythmias.

Systemic Hypertension

This is another significant cardiovascular side effect of ibrutinib. This differs from other adverse effects of ibrutinib in two aspects. Hypertension is a class effect of all BTK inhibitors. Its incidence increases with time, unlike other adverse effects which decrease after the 1st 6 months of therapy.[9]

Recommendations

1. Monthly blood pressure monitoring is indicated. Start anti-hypertensives as indicated
2. No need to reduce or interrupt ibrutinib.

Arthralgia

It is a significant cause of worsening quality of life and treatment interruption in patients on ibrutinib. The mechanism is unknown, but it is generally of low grade and self-limiting (few months).

Recommendation

1. Nonsteroidal anti-inflammatory drugs are contraindicated due to the risk of bleeding
2. Paracetamol and a short course of steroids can be tried
3. Temporary interruption of ibrutinib if symptoms fail to resolve.

Skin Toxicity

Two types of rash have been reported: a palpable pruritic rash due to off-target EGFR inhibition by ibrutinib, which may require topical steroids. And a nonpalpable petechial rash related to platelet dysfunction, which is generally self-resolving.[23]

Recommendation – no need to interrupt ibrutinib.

Leukostasis

It is rarely reported.

Recommendation: If lymphocyte count >400,000/μL – consider temporarily withholding ibrutinib.[7]

Cytopenias

Treatment-emergent Grade ¾ cytopenias have been reported with ibrutinib. Neutropenia is the most common (29%), followed by thrombocytopenia (17%) and anemia (9%).

Recommendation: Consider monthly complete blood count monitoring.[6]

Resistance to Ibrutinib

Chronic lymphocytic leukemia

CLL cells have an exquisite sensitivity to ibrutinib. Resistance to ibrutinib can be primary, seen with Richter transformation. This is usually seen within the first 12 months of therapy. On the other hand, those who develop secondary resistance due to mutations, present in the late treatment phase beyond 24 months.[24]

The presence of BCL6 abnormalities, complex karyotype, or baseline del(17p) is associated with an increased risk of acquired mutations.[25] The common secondary mutations are (i) mutation at the ibrutinib binding site on BTK (C481S), which leads to reduced binding, and (ii) activating mutations in PLCG2 (R665W, L845F, and S707Y), which leads to pathway activation that is independent of BTK. The other uncommon mutations include deletion 8p, 2p gain, and XPO1 overexpression.[26,27]

The incidence of mutations increases with time. Woyach *et al*. reported the incidence of mutations at 2 years, 3 years, and 4 years as 5%, 10.8%, and 19.1%, respectively. Mutations in BTK and PLCG2 are detected in 80%–90% of CLL cases at the time of disease progression.[28]

The mutation is analyzed by next-generation sequencing in peripheral blood, bone marrow aspirate, or even lymph node biopsy sample. Commercial mutation testing is currently unavailable in India.

Mantle cell lymphoma

Mutations are seen more commonly than with CLL and involve multiple resistance pathways including, C481S BTK mutation, enhanced PI3K-AKT signaling, CDK4 resistance pathway activity, and BCR independent growth via an activating RAS mutation.[29]

Waldenström's macroglobulinemia

Mutations are uncommon and predominantly involve C481S BTK mutation.

Chronic Lymphocytic Leukemia

The therapy of CLL has progressed over the years, from chemo-only regimens such as alkylating agents and purine analogs to chemoimmunotherapeutic combinations.

However, the outcomes are still suboptimal in those with deletion 17p. Ibrutinib is now recommended as the first-line therapy for CLL with 17p deletion.[30] The NCCN also recommends it as one of the first-line agents across age groups and irrespective of comorbidities in CLL without 17p deletion, thus highlighting its efficacy in CLL.

The landmark trials in CLL are summarized in Table 4 and the drawbacks of Ibrutinib in CLL have been summarised in Table 5.

Ibrutinib Adherence Issues

In chronic leukemia such as CML, adherence has shown to have a strong correlation with the efficacy. Similar data are emerging on ibrutinib. Analysis of the RESONATE trial data shows that dose intensity <95% is associated with poorer progression-free survival (PFS).[40] Similarly, real-world data suggest that drug interruption >14 days is associated with inferior OS.[41]

Reduced-Dose Ibrutinib

In an original article on ibrutinib, 420 mg was determined as the dose required to achieve ≥95% saturation of BTK receptors. The authors also contended that because ibrutinib is an irreversible BTK inhibitor – the percentage of saturation is not linked to drug efficacy.[42] Taking this concept forward, there have been few retrospective studies that have shown that a lesser dose of ibrutinib has equal efficacy.[43,44] There are emerging data that reduced dose of ibrutinib after one full dose cycle has equivalent biological activity.[45] However, in the absence of prospective trial data – reduced-dose ibrutinib is not recommended at present.

Tumor Debulking

In the case of bulky disease, few experts advocate debulking with two cycles of single-agent bendamustine before starting ibrutinib. Bulky disease has been defined as lymph node size ≥5 cm and/or lymphocyte count ≥25 × 10^9/L.[46] While debulking is not universally practiced, it is indicated for rapidly growing, bulky disease in the relapsed setting.[47]

Therapy after Ibrutinib Failure

The treatment options post ibrutinib failure are dismal with a median survival of 18 months without Richter's transformation and 3.5 months with Richter's

Table 4: Seminal clinical trials in chronic lymphocytic leukemia

Trial/phase	*n*	Patient profile	Drug	ORR	CR	MRD	PFS	Key message
Resonate Phase III[31]		Relapsed setting	IB versus ofatumumab	43% versus 4.1%	0% versus 0%	N/A	PFS not reached versus 8.1 months	FDA approval for relapsed CLL and 17p deleted CLL
RESONATE-2 Phase III[32]	296	Frontline, age >65	IB versus chlorambucil	82% versus 35%	4% versus 2%	N/A	PFS: Not reached versus 18.9 months	FDA approval for treatment-naïve CLL
HELIOS Phase III[33]	578	Relapsed	BR + IB versus BR + placebo	83% versus 68%	10% versus 3%	13% versus 5%	PFS not reached versus 13.3 months	Higher MRD negativity when IB combined with CIT
Burger *et al*. Phase II[34]	206	Relapsed and high risk frontline	IB versus IB + R	92% versus 92%	20% versus 26%	4.8% versus 0.9%	3 years PFS 86% versus 87%	No benefit of adding rituximab to IB in elderly
ALLIANCE A041202 study Phase III[35]	547	Age >65 Frontline CLL	IB versus IB + R versus BR	93%/94%/81%	7%/12%/26%	1%/4%/8%	2 years PFS 87%/88%/74%	IB superior to BR in elderly CLL
Illumniate Phase III[36]	229	Age >65 CLL with comorbidities	IB + obinutuzumab versus Clb + obinutuzumab	88% versus 73%	19% versus 8%	35% versus 25%	mPFS not reached versus 19 m	Higher undetectable MRD when IB combined with immunotherapy
E1912 Phase III[37]	529	Age <70 Frontline CLL	IB + R versus FCR	96% versus 81%	17% versus 30%	85% versus 59%	3 years PFS 89% versus73%	Unmutated IGHV - FCR is equivalent to IB + R
Jain *et al*. Phase II[38]	80	High risk CLL	IB + venetoclax	100%	88%	61%	1 year PFS 98%	Synergistic action. Fixed-duration therapy
Rogers *et al*. Phase II[39]	25	Frontline CLL	IB + venetoclax + obinutuzumab	100%	50%	58%	N/A	Final results awaited

IB – Ibrutinib; R – Rituximab; Clb – Chlorambucil; BR – Bendamustine rituximab; ORR – Overall response rate; PFS – Progression-free survival; uMRD – Undetectable MRD; FDA – Food and Drug Administration; CLL – Chronic lymphocytic leukemia; MRD – Minimal residual disease; CIT – Chemoimmunotherapy; N/A – Not available; CR – Complete response; mPFS – median progression free survival; IGHV – ImmunoGlobulin heavy chain variable region gene; FCR – Fludarabine cyclophosphamide rituximab

transformation.[22,48] Venetoclax is the treatment of choice after the failure of ibrutinib, with trials showing 70% response rate in this setting.[49] However, the reverse is not true, and there is only limited data on the use of ibrutinib after venetoclax failure.[50]

Ibrutinib – Combination Therapy

Combination with Anti-CD20 Antibody

The study by Burger *et al*. and the A041202 study failed to show any benefit of combining rituximab with ibrutinib.[35,36] Obinutuzumab has superior efficacy in comparison to rituximab in the therapy of CLL. The data on the synergism of obinutuzumab with ibrutinib are awaited.[39]

Ibrutinib with Venetoclax

Venetoclax has proven efficacy in CLL as a single agent with a deep response (62% MRD negative at 2 years). The activity of the two drugs are complementary – while ibrutinib acts on the lymph nodes, venetoclax acts on the blood and the bone marrow. A decrease in MCL1 (myeloid cell leukemia 1) levels by ibrutinib aids the cell kill by venetoclax. The other advantages of this combination are a nonoverlapping side effect profile and the benefit of a 2 year-fixed duration therapy.[38,39]

Other ongoing studies on combination with ibrutinib include triplet therapy with ibrutinib + venetoclax + obinutuzumab studies (EA9161 and A041702)[51,52] and a combination of PI3K inhibitor + ibrutinib + CD20ab.[53] Ibrutinib is also effective in combination with CAR-T cells.[54]

Table 5: Disadvantages of ibrutinib in chronic lymphocytic leukemia therapy

Indefinite therapy
A relatively small proportion of patient achieve complete remission
20% develop ibrutinib resistance
30% develop severe toxicity leading to drug discontinuation

The use of Ibrutinib for other conditions is summarised in Table 6.

Mantle Cell Lymphoma

Ibrutinib is a promising drug for relapsed MCL. It has shown response in nearly 2/3rd of patients with R/R MCL, which is comparable to intensive chemotherapy regimens such as ESHAP, hyperCVAD, and R-ICE.[60-63] It has good CNS penetration and has been proven to be effective in CNS involvement by MCL.[64] The adverse effect profile is also comparable to CLL therapy, and redistribution lymphocytosis is also observed.

The disadvantages include the lack of long-term survival, owing to loss of response (median duration of 17.5 months). Strategies to overcome this shortcoming include combination with venetoclax or using ibrutinib as a bridge to allogeneic transplantation.[65,66]

Waldenström Macroglobulinemia

Three prospective Phase II trials done in WM, have shown excellent results with both ORR and 18th month PFS over 90%.[56,57,67] The response is demonstrated irrespective of whether it is in the upfront setting, relapsed setting, and rituximab refractory setting. When combined with rituximab, it has the advantage of decreasing the risk of IgM flare. The need to add rituximab to ibrutinib is questioned, but currently, there is no data available against this combination for WM.[68] Ibrutinib therapy in WM has a few unique features such as the risk of IgM rebound on ibrutinib discontinuation,[69] and the variability in response based on the molecular status of WM-MYD88 L^{265P}CXCR4^{WT} has the best response, while MYD88^{WT}CXCR4^{WT} has the worst response [Table 4].[56]

Marginal Zone Lymphoma

Chronic antigen stimulation plays a major role in the pathogenesis of MZL, and ibrutinib through its BCR inhibition is a natural choice of therapy. The pivotal trial

Table 6: Key trials for other conditions

Trial/phase	*n*	Disease profile	Drug	Results	Key message
PCYC-1104-CA trial Phase II[55]	115	MCL Relapsed/refractory	IB - single arm	ORR: 68% CR: 21%	FDA granted accelerated approval
Treon *et al*. Phase II[56]	63	WM Previously treated	IB - single arm	ORR: 90.5% OS: 95.2%	FDA approval in WM
Treon *et al*. Phase II[57]	31	WM Frontline	IB - single arm	ORR: 100% MRR: 83% 18 months OS: 100%	MYD88L265PCXCR4WT subset had the best response
Noy *et al*. Phase II[58]	60	MZL Relapsed/refractory	IB - single arm	ORR was 48%, CR rate was 3%	1st drug to be approved specifically for MZL
Study 1129 Phase II[59]	42	cGVHD Steroid refractory	IB - single arm	ORR was 76%, 71% of responders had sustained response ≥20 weeks	FDA approval for steroid-refractory cGVHD

IB – Ibrutinib; ORR – Overall response rate; MRR – Major response rate; OS – Overall survival; MZL – Marginal zone lymphoma; WM – Waldenström's macroglobulinemia; MCL – Mantle cell lymphoma; CR – Complete response; FDA – Food and Drug Administration

by Noy *et al*. showed that it had good efficacy in cases that relapse after rituximab-based therapy. The fascinating aspect of this study was the difference in efficacy as per disease subtype. Splenic MZL had the best PFS of 19.4 months, while nodal MZL had the lowest PFS of 8.3 months.[58]

Diffuse Large B-Cell Lymphoma

Ibrutinib has proven efficacy in non-GCB-type DLBCL, but the combination of ibrutinib with R CHOP has shown poor tolerability, especially in those over 60 years.[70] In contrast, the combination of lenalidomide with ibrutinib has shown synergism in non-GCB DLBCL trials – both in upfront and relapsed settings. Further results are awaited.[71]

Other Malignancies

Ibrutinib remains a viable therapeutic option for rare indolent lymphomas such as B-PLL which have a higher TP53 mutation positivity.[72] Similarly, variant HCL which is relatively resistant to cladribine, responds well to ibrutinib.[73] This versatile drug has also shown some efficacy in relapsed PCNSL.[74]

Ibrutinib has failed to show any major benefit in relapsed myeloma and follicular lymphoma.[75,76] The drug modulates the tumor microenvironment and hence, it has been tried with some success in varied nonhematological malignancies including gynecological malignancies, pancreatic carcinoma, prostate cancer, and glioblastoma multiforme.[77-80]

Ibrutinib in the Transplant Setting

Ibrutinib has been used in three scenarios associated with hematopoietic stem cell transplantation (HSCT).

Bridge to Allogeneic Hematopoietic Stem Cell Transplantation

The EBMT recently published the transplant data of CLL and MCL patients, who received ibrutinib pretransplant. Ibrutinib did not adversely affect engraftment or GVHD rates. In CLL patients treated with ibrutinib – ibrutinib failure or duration of ibrutinib <8 months was associated with early relapse, thus highlighting the transient nature of the response to ibrutinib in CLL. In contrast, when ibrutinib is used as a bridge to HSCT in MCL, it was associated with a good response.[81]

Chronic Graft versus Host Disease

Miklos *et al*. showed that ibrutinib was effective in steroid-refractory cGVHD, where it was equally effective for gut GVHD, skin GVHD, and oral GVHD. Ibrutinib was approved by the FDA based on this study's results. It was interesting to note that indefinite therapy was given even in the posttransplant setting, although 71% had discontinued ibrutinib at 14 months in this study.[59]

Ibrutinib as Salvage PostAllo Hematopoietic Stem Cell Transplantation

EBMT studied the effectiveness of ibrutinib post-HSCT when it was used for indications other than for managing GVHD. The study demonstrated a 71% overall response rate in CLL patients who relapse after allogeneic HSCT. Its safety and efficacy were comparable to nontransplanted patients with high-risk disease.[82]

Cost-Effectiveness of Ibrutinib BR

Assuming a body surface area of 1.62 m^2, the cost of six cycles of bendamustine rituximab (generic brand) is approximately Rs. 330,000. The cost of 1-year therapy with ibrutinib (innovator) is five times the cost of BR therapy.[43] However, the cost of recently introduced generic ibrutinib is Rs. 346,000, which is equivalent to BR therapy.

Conclusion

The development of ibrutinib has tremendously improved the therapy of CLL. However, the discontinuation of treatment due to loss of initial response and intolerance remains an issue. The development of good postibrutinib strategies will define this era of targeted therapy.

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Conflicts of interest

There are no conflicts of interest.

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