bjh review

Breaking good: the inexorable rise of BTK inhibitors in the treatment of chronic lymphocytic leukaemia

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Summary

Although expressed in several haematological lineages and involved in multiple different signalling pathways, Bruton tyrosine kinase (BTK) plays an indispensible role in B cells in signalling from the B cell receptor (BCR) for antigen. Many B cell malignancies remain dependent on constitutive BCR signalling, making BTK a functional therapeutic target. Several BTK inhibitors (BTKi) with different kinomes and modes of action are being assessed clinically. This review documents the efficacy and toxicity of BTKi in chronic lymphocytic leukaemia (CLL). Clinically, the furthest in development is ibrutinib (trade name, Imbruvica), an irreversible BTKi, which has shown spectacular preliminary efficacy, with rapid reductions in lymph nodes accompanied by peripheral blood lymphocytosis. The lymphocytosis resolves slowly and most patients do not enter a complete remission. Nevertheless, it is possible to maintain many CLL patients, even those with adverse cytogenetic features, on drug for many months with minimal toxicities, thus potentially transforming the therapeutic paradigms for CLL. The efficacy, lack of toxicity and oral administration of BTKi will ensure their adoption in a wide range of B cell malignancies. An outstanding challenge is to incorporate BTKi with other precision medicines in a mechanism-based manner in order to dispense with conventional chemotherapy.

Keywords: chronic lymphocytic leukaemia, Bruton tyrosine kinase, ibrutinib, B cell receptor signalling.

If the multi-billion dollar industry that has developed since the 'war on cancer' was announced by Richard Nixon in 1971 (Sporn, 1997) is eventually to succeed in 'eliminating the suffering and death from cancer' (von Eschenbach, 2006), then it must provide tools that allow either eradication or long-term control of disease with minimal toxicity. In terms of the malignancies of mature B cells, significant progress has been made and there is now a plethora of 'precision medicines' including both engineered antibodies and targeted small molecules that are having great therapeutic impact even in early phase clinical trials (Dyer *et al*, 2013).

One class of small molecule inhibitor currently arousing intense interest comprises compounds targeting Bruton tyrosine kinase (BTK). Importantly, BTK is not a genetically-defined therapeutic target; there are no mutations in the *BTK* gene or gene fusions that result in constitutive activity. Rather, BTK is defined functionally as a therapeutic target, playing a key role in several pathways that maintain B cell survival. The efficacy of BTK inhibitors (BTKi) in several forms of mature B cell malignancy has been spectacular, resulting in the first-in-class BTKi (Ibrutinib; Pharmacyclics, Sunnyvale, CA, USA) being awarded 'Breakthrough Drug' status by the US Food and Drug Administration (FDA) for mantle cell lymphoma (MCL), CLL and Waldenstrom macroglobulinaemia (Dolgin, 2013); breakthrough drug status is given if preliminary clinical evidence indicates the drug may offer a substantial improvement over available therapies for patients with serious or life-threatening diseases. A product licence for ibrutinib, for the treatment of relapsed MCL, was awarded by the US FDA on 13 November 2013 and for relapsed CLL on 11 February 2014; at the time of writing, similar licences are anticipated imminently in Europe.

This review addresses the rationale for targeting BTK in CLL, the nature and mode of action of BTKi and the data emerging from clinical trials in CLL, alone and in combination with other agents. Despite their huge promise and huge enthusiasm for their use from both patients and clinicians alike, there remain several barriers to the incorporation of these novel agents into CLL therapy.

An overview of BTK structure and functions

BTK takes its name from Colonel Ogden C. Bruton (1908–2003), an American Army paediatrician based at the Walter Reed Army Hospital in Washington DC, who, in 1952, described a condition now referred to as X-linked agammaglobulinaemia, following the study of an 8-year-old boy, Joseph S. Holtoner, Jr., who had recurrent pneumonia and

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absence of gamma globulin in his serum (Bruton, 1952). Dr Bruton and his discovery were featured in 'TIME' magazine 18 May 1953. It was noted that all patients were boys; disease identification followed the development of successful antibiotic therapy for recurrent bacterial infections. Forty years later, following extensive mapping experiments, the gene responsible for this condition (*BTK*), was cloned and characterized (Tsukada *et al*, 1993; Vetrie *et al*, 1993). Mapping to chromosome Xq21.3-q22, *BTK* encodes a kinase of the TEC subfamily (Yu & Smith, 2011; and other articles in that issue). Collectively, these kinases (BTK, ITK, BMX, TXK and TEC) are characterized by five structural domains including PH (pleckstrin homology) mediating phosphatidylinositol (3,4,5)-trisphosphate (PIP3) binding, TEC homology (BH), SH3 (Src homology 3), SH2 (Src homology 2) and kinase domains (Fig 1). The crystal structures of the major BTK domains have been solved (Mao *et al*, 2001; Marcotte *et al*, 2010). These structures have been of fundamental importance in terms of the design of targeted inhibitors, especially the irreversible inhibitors, such as ibrutinib, AVL-292/CC-292 and ONO-4059 (Kuglstatter *et al*, 2011). BTK is localized predominantly in the cytoplasm (but interestingly, also in the nucleus) with translocation to the plasma membrane *via* the PH domain following PIP3 binding, for phosphorylation and activation. Within BTK there are two major tyrosine phosphorylation sites. Phosphorylation of tyrosine (Tyr)551 within the kinase domain regulates the transition between active (open) and inactive (closed) states. Phosphorylation of Tyr551 occurs on localization to the membrane by SRC family kinases (LYN/FYN/BLK) or SYK kinase. Conformational change then enables auto-phosphorylation at Tyr223. Once activated, BTK can then phosphorylate phospholipase Cγ2, leading to calcium mobilization (King & Freedman, 2009) and subsequent activation of downstream signalling pathways, cytoskeletal rearrangements and transcriptional pathways (including NF-κB, NFAT and ARID3A) involved in proliferation, cell survival and migration (Fig 1). Over 600 unique inherited *BTK* mutations have been described that lead to profound defects in B cell development (failure of development of pro to pre B cells) and immunoglobulin production (Valiaho *et al*, 2006; http://structure.bmc.lu.se/idbase/BTKbase/). BTK mutations fall within all domains with the exception of the SH3 domain and many affect crucial residues involved in either ATP binding or in the catalytic site; others affect substrate recognition. Affected boys have normal levels of pre-B cells in their bone marrow but virtually no circulating mature B lymphocytes, with a resultant lack of immunoglobulins of all classes and recurrent bacterial infections in the first few years of life. Interestingly, mice with identical *Btk* mutations have a much milder phenotype, indicating a

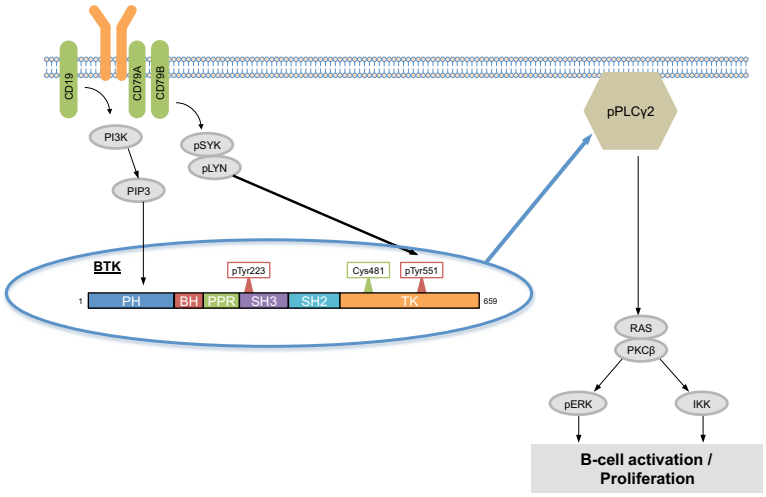

Fig 1. BTK and its involvement in BCR signalling. Bruton tyrosine kinase (BTK) comprises several domains including: (i) pleckstrin homology (PH) domain. Mediates binding to inositol polyphosphate and phosphoinositides, leading to targeting of BTK to the plasma membrane. Plasma membrane localization is a critical step in the activation of BTK. (ii) BTK homology (BH) domain. Contains a highly conserved zinc finger motif that mediates Zn^{2+} ion binding necessary for protein stability. (iii) Polyproline (PPR) domain. (iv) Src homology (SH3 and SH2) domains. The SH2 domain of BTK binds to the B cell adapter protein BLNK, which is required for full BTK activation. (v) Tyrosine kinase (TK) domain. Unphosphorylated BTK is catalytically inactive. As shown in the figure, full activation of BTK requires both phosphorylation and binding of PIP3. Following BCR engagement and activation, and following PIP3 binding, BTK translocates to the plasma membrane, where it is phosphorylated at Tyr551 by LYN and SYK, leading to autophosphorylation of Tyr223. Once bound to BLNK, BTK phosphorylates PLCG2 at several sites, leading to calcium mobilization and activation of the protein kinase C (PKC) family members and other effectors including RAS and lead to NFκB activation and phosphorylation of ERK. The BTK inhibitors ibrutinib, CC-292 and ONO-4059 all bind irreversibly to Cys481 within the ATP binding site of the BTK kinase domain, thus preventing BTK activation. In contrast, the highly specific BTKi, CGI-1746, binds to the ATP binding pocket of BTK and stabilizes the non-phosphorylated form of the protein by internalizing Tyr551. Apart from its role in BCR signalling, BTK is also implicated in cytokine and Toll receptor signalling pathways (not shown).

species-specific functional redundancy; combined inactivation of both *BTK* and *TEC* is necessary to produce a similar phenotype in mice.

Although recent focus has been on the role of BTK in terms of modulating signalling from the BCR as outlined below, BTK is, in fact, activated in response to a very broad range of growth/differentiation stimuli in haemopoietic tissues, including growth factor receptors, cytokine receptors, G-protein coupled receptors and integrins (Qiu & Kung, 2000). BTK is implicated in the control of several pathways of central importance to mature B cells. Moreover, BTK is expressed in all bone marrow-derived cell lineages, with the exception of T lymphocytes and plasma cells (de Weers *et al*, 1993; Genevier *et al*, 1994; Smith *et al*, 1994). In terms of these other lineages the functions of BTK are relatively unexplored, but recent data indicate key functions in myeloid cells (Honda *et al*, 2012). Recent exciting *in vitro* data indicate that BTK may be a therapeutic target in acute myeloid leukaemias (Rushworth *et al*, 2014) as well as B cell malignancies. In macrophages, BTK functions downstream of several toll-like receptors and regulates apoptotic cell uptake (Byrne *et al*, 2013). These and other observations may also have important clinical implications in terms of design of BTKi combination studies, for example, with therapeutic monoclonal antibodies dependent on macrophages for their clinical efficacy. BTKi may also interfere with platelet activation (Byrd *et al*, 2013a; Hsu *et al*, 2013; Rushworth *et al*, 2013). Rushworth *et al* (2013) showed that ibrutinib impaired the platelet activation in response to collagen and ADP; however, the clinical significance of these observations is not clear (Farooqui *et al*, 2012). Finally, BTK is highly homologous to the interleukin-2 inducible T cell kinase (ITK) expressed in T cells, a homology that may be of therapeutic relevance (Dubovsky *et al*, 2013). Inherited mutations in *ITK* predispose to viral infections, including Epstein–Barr virus (EBV) infection as well as EBV-driven lymphoproliferative conditions (Huck *et al*, 2009; Stepensky *et al*, 2011).

Collectively, these data do not appear to augur well for targeting BTK therapeutically. The expression of BTK in multiple haemopoietic lineages, the involvement of BTK in multiple different pathways, and the complete block of normal B cell development in individuals with constitutional *BTK* mutations suggest that BTK inhibition might be catastrophic! However, all of the above appear to be trumped by functional data concerning the central role of BTK activity in the maintenance of several forms of mature B cell malignancy.

Functions of BTK in malignant B cells; BTK as a potential therapeutic target

In mouse models, BCR signalling is vital for the survival of normal mature B cells (Kraus *et al*, 2004): interestingly, in mice this defect is rescued by phosphatidylinositide 3-kinase (PI3K) rather than BTK signalling (Srinivasan *et al*, 2009). In human B cell malignancies, maintained BCR signalling has been shown to play an essential role in the survival of the activated B cell subtype of diffuse large B cell lymphoma (DLBCL) and in CLL (please see two recent reviews, Burger & Chiorazzi, 2013; Young & Staudt, 2013). In activated B cell (ABC)-DLBCL, constitutive BCR signalling is largely driven by somatic mutations in key domains of signalling molecules including CD79A/B and CARD11 (Davis *et al*, 2010). In CLL however these mutations are not present, but a fascinating recent finding indicates that the configuration of the BCR itself may drive antigen-independent cell-autonomous signalling (Duhren-von Minden *et al*, 2012). Inhibition of BTK may therefore be effective therapy in all cases of CLL rather than just with maintained signalling capacity following BCR cross-linking *in vitro* (Apollonio *et al*, 2013).

However, the above scenario is complicated by the involvement of BTK in other signalling pathways controlling B cell migration and motility. Mature lymphocytes are not static; they are constantly moving between blood and tissues (Gowans & Knight, 1964). For normal lymphocytes this process enables immune surveillance; for malignant lymphocytes it offers a protective niche in which to receive survival and proliferation signals from the microenvironmental and soluble factors within the lymph node. Lymphocyte movement is not random and depends on a complex process of signalling pathways involving adhesion molecules and chemokines, which ultimately control the cytoskeleton. Two such pathways of particular importance are the chemokine receptor-ligand pathways CXCR4-CXCL12 and CXCR5-CXCL13. BTK is known to be important for B cell migration and homing (Ortolano *et al*, 2006; de Gorter *et al*, 2007), and is activated upon chemokine binding to CXCR4 and CXCR5 through direct interaction with the chemokine receptor G protein subunits (Jiang *et al*, 1998; Lowry & Huang, 2002). Thus, BTKi may have a significant effect on lymphocyte homing and recirculation; this has been observed clinically in CLL patients receiving BTKi, as discussed below. The relative importance of BTKi-mediated blockade of the various different pathways will presumably vary from patient to patient, and moreover in CLL cells at different anatomical locations.

Pharmacological development of BTKi

As is so often the case in drug development, there are several BTKi currently in clinical trial or in late preclinical development. Some of the BTKi being assessed are listed in Table I; Ibrutinib (Pharmacyclics) is furthest along in terms of clinical development but there are a currently a number of others undergoing clinical trials including AVL-292/CC-292 (Celgene, Summit, NJ, USA) and ONO-4059 (ONO Pharmaceuticals, Osaka, Japan). Whilst this plethora of new molecules is of considerable scientific and clinical interest and reflects the activities of unfettered market forces, one must question the logic of commercially developing so many molecules

Table I. BTKi currently in clinical trial or preclinical development.

Molecule	Company	Irreversible inhibitor?	BTK IC_{50}	BTK specific?	Clinical development	Clinical trials	References
Ibrutinib	Pharmacyclics/Jansen	Yes	0·5 nmol/l	No – broad kinome	Multiple Phase II and Phase III clinical trials		See text
AVL-292/CC-292	Avila/Celgene	Yes	<0·5 nmol/l	Yes	Phase II clinical trial	NCT01766583 With Lenalidomide in ABC-DLBCL	See text
ONO-4059	Ono Pharma	Yes	2·2 nmol/l	Yes	Phase I clinical trial	NCT01659255 Dose escalation in B cell malignancies	Salles *et al* (2013) and Rule *et al* (2013)
HM71224	Hanmi Pharma	NK	NK	Yes	Phase I in normal individuals	NCT01765478	NK
GDC-0834	CGI Pharma Genentech	No	5·9 nmol/l	NK	Phase I normal individuals		Liu *et al* (2011)
CGI-1746	CGI Pharma	No	1·9 nmol/l	Yes	Preclinical		Di Paolo *et al* (2011)

BTK, Bruton tyrosine kinase; BTKi, Bruton tyrosine kinase inhibitor; IC_{50}, 50% inhibitory concentration; ABC-DLBCL, activated B cell-diffuse large B cell; NK, not known.

against the same target. Which might be best clinically is quite unclear, and given the clinical success of ibrutinib may well be impossible to assess. The chemical structures of the three irreversible BTKi are very similar and yet the kinomes of each molecule are very different.

The development of ibrutinib is of interest for at least two reasons. Firstly, and most importantly, ibrutinib is an irreversible BTKi that binds covalently to BTK (Pan *et al*, 2007). A series of highly selective and irreversible BTKi were developed at Celera using a bioinformatics approach using the crystal structures of BTK. These molecules inactivate BTK by covalent binding to Cys481 near the ATP binding domain of BTK and thus inhibited phosphorylation at Tyr223. The lead molecule (PCI-32765) was tested in *in vivo* models of both rheumatoid arthritis and lymphoma (using a spontaneously occurring canine lymphoma model) and showed considerable activity (Honigberg *et al*, 2010). Historically, the pharmaceutical industry has been wary of irreversible kinase inhibitors because of concerns over possible toxicity, particularly so in kinases with long protein half-lives. (Interestingly, BTK is a long-lived protein with a half-life in B cells of over 8 h). However, there are now an increasing number of irreversible kinase inhibitors entering the market, including afatinib an irreversible inhibitor of EGFR (Sanderson, 2013). The second interesting aspect about ibrutinib is that its kinome is very broad and includes several other kinases with pivotal roles in normal and malignant B cell signalling, including numerous SRC kinase family members including LYN (Pan *et al*, 2007). Not unsurprisingly, given the close homology of the two proteins, ibrutinib irreversibly inactivates ITK as well as BTK (Dubovsky *et al*, 2013). One of the implications of this finding might be a role for ibrutinib in T cell malignancies dependent on ITK signalling as well as those with ITK fusions (Streubel *et al*, 2006; Pechloff *et al*, 2010). Less positively, it is difficult to reconcile the lack of observed toxicity seen in patients taking ibrutinib for many months with this broad kinome, especially perhaps in patients immunocompromised by their disease and prior therapies.

A variety of more specific BTKi have been developed and three of these are currently undergoing clinical trials in B cell malignancies. Some of these are shown in Table I. AVL-292/CC-292 and ONO-4059 are both irreversible inhibitors, which are closely related to ibrutinib structurally but are considerably more specific in terms of other kinases inhibited; both are being assessed in patients with B cell malignancies. ONO-4059 is in early phase I development but initial results presented at the American Society of Hematology (ASH) annual meeting in 2013 indicate comparable activity to ibrutinib in CLL with possibly less toxicity; significant efficacy was also observed in MCL (Salles *et al*, 2013; Rule *et al*, 2013). Data with AVL-292/CC-292 in CLL is given below and with twice daily dosing suggests improved nodal responses (Harb *et al*, 2013). The combination of AVL-292/CC-292 and lenalidomide in ABC-DLBCL is of interest, given that both molecules have significant activity against this disease subtype (Yang *et al*, 2012; Vose *et al*, 2013; NCT01766583). This combination is also being assessed in CLL (NCT01732861); it is a mechanistically and financially logical combination, given that both lenalidomide and CC-292 are now owned by Celgene. Another BTKi, CGI-1746 [CGI Pharmaceuticals (Branford, CT, USA) (now part of Gilead)] is highly BTK-specific and may have unique and potentially advantageous properties. CGI-1746 binds to the ATP-binding pocket of BTK and stabilizes the non-phosphorylated form of the protein by internalizing the crucial residue Tyr551, which has to be phosphorylated

for BTK activation. CGI-1746 therefore has exquisite sensitivity for BTK (Di Paolo *et al*, 2011). Whether this molecule is now being developed for clinical use is not clear.

There are insufficient data to compare the BTKi even indirectly at the current time. Paradoxically, given the data from the clinical studies to date, the 'dirtier' inhibitor, ibrutinib might possibly have significant advantages.

Clinical studies with BTKi

Ibrutinib as single agent has been used both in elderly patients (≥65 years) with treatment-naïve CLL and those with relapsed and refractory disease. A phase Ib-II trial was recently reported for relapsed and refractory CLL (Byrd *et al*, 2013b). Eighty-five patients considered to be 'high risk' were treated with either 420 mg (51 patients) or 840 mg (34 patients). The overall response rate (ORR) was 71% in both cohorts [two complete responses (CR) and 34 partial responses (PR)] with a further 20% (420 mg cohort) and 15% (840 mg cohort) achieving a PR with lymphocytosis. The response was independent of the number of previous therapies or high-risk features, including 17p 13 deletion. At 26 months, progression-free survival (PFS) was estimated at 75% and OS at 83%. A lymphocytosis was observed in 78% of patients. Ibrutinib was very well tolerated; however, the higher dose was associated with more adverse events leading to discontinuation of treatment (two patients on 420 mg and four patients on the 840 mg dose). Perhaps not surprizingly in this patient group, pneumonia was the most common grade 3 or higher adverse event, seen in 10 patients, and infections were seen more commonly early in treatment. Interestingly, despite the low levels of immunoglobulins seen in patients with the genetic mutation of *BTK*, immunoglobulin levels remained relatively stable during treatment. Indeed, IgA and IgM serum levels increase on treatment, signifying recovery of humoral immunity (Farooqui *et al*, 2013). The treatment-naïve arm of this trial in patients older than 65 years ($n = 31$) was updated at the International Workshop on Chronic Lymphocytic Leukaemia in 2013 (iwCLL2013): with a median follow up of 22·1 months, the ORR was 71% (CR 13%) with a 96% PFS (O'Brien *et al*, 2014).

An unanticipated finding was that ibruitinib induced a prompt lymphocytosis in the peripheral blood. A similar effect was observed in patients receiving PI3 delta kinase inhibitors (reviewed in Macias-Perez & Flinn, 2013) as well as CXCR4 antagonists. In ibrutinib-treated CLL patients the lymphocytosis is usually seen by 7 d, peaking within 4 weeks and then slowly decreasing with time, which is generally slower than that seen with treatment in MCL. The lymphocytosis is not restricted to subtypes of CLL but patients with unmutated immunoglobulin variable-region heavy chain (*IGHV*) gene segments had an earlier resolution of lymphocytosis compared to patients with mutated *IGHV* rearrangements (median 6·4 vs. 14·8 months) (Byrd *et al*, 2013a). It is not yet clear whether the rate of fall in lymphocyte count will perhaps become a prognostic factor as important as lymphocyte doubling time.

What are the practicalities?

Ibrutinib is given orally once a day. In CLL patients, the optimal dose, determined from the above trials and being taken forward in future trials, is 420 mg. Given the broad expression of BTK in haematological cells and the ibrutinib kinome, it is surprising that the drug is so well tolerated. Toxicities are very manageable on an out-patient basis with the most common treatment-related adverse event being mild to moderate diarrhoea, fatigue and nausea, with pneumonia more commonly seen in CLL patients. Haematological grade 3 or higher neutropenia, thrombocytopenia and anaemia are seen in 10–20% of patients with previously treated CLL and these improve with treatment. Bleeding is seen in a subset of patients and current trials exclude the concurrent use of warfarin but not other anticoagulant therapies.

How will ibrutinib compare to other single agents?

Two randomized, multicentre phase III trials are currently ongoing to address this question. RESONATE-2 is comparing chlorambucil against ibrutinib in a 1:1 randomization in treatment–naïve CLL/SLL patients older than 65 years (NCT01722487), whilst RESONATE compared the novel CD20 monoclonal antibody ofatumumab against ibrutinib in relapsed/refractory CLL/SLL patients (NCT01578707). The latter study was stopped early by the data monitoring committee after an an interim analysis showed that patients on ibrutinib had a statistically significant improvement not only in PFS (the primary study end point), but also in OS (a secondary end point), when compared with ofatumumab (http://www.pmlive.com/pharma_news/j_and_js_imbruvica_tops_arzerra_in_phase_iii_trial_531853 and please see also http://www.btktrials.com.)

Will remission be achieved using single agent ibrutinib?

The present indication is that there are very few complete responses with ibrutinib (2% in previously treated CLL, 13% in treatment naïve CLL) and progression is rapidly seen when treatment is interrupted. However, most patients continue to have an ongoing response with continued treatment and the role of combination therapy to improve responses, with the aim of attaining a minimal residual disease (MRD) negative response without significant toxicity is keenly debated.

What about the chance of developing resistance to BTK inhibition?

In CLL patients who had developed resistance to ibrutinib, comparative DNA sequence analysis of the genome was performed in samples at baseline and at disease progression.

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