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SUPPLEMENT ARTICLE

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New drugs and pharmacological interactions in real life

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Abstract

A high number of new drugs have entered clinical development and many of them have recently been approved for patients with lymphoid malignancies. The availability of new drugs offers additional treatment options, but it also requires particular attention for the emergence of adverse events. In addition, new drugs may also have interactions with other drugs, which could further increase the risk of toxicities or result in decreased efficacy. Here we review potential drug interactions for nonchemotherapy new drugs approved for patients with lymphoid malignancies.

KEYWORDS
drug interactions, lymphoid malignancies, new drugs

1 | INTRODUCTION

Over the last years, several new drugs including small molecules, monoclonal antibodies (either naked or conjugated), and more recently adoptive cell therapies have been approved for the treatment of patients with lymphoid malignancies.[1–8] With the exception of chimeric antigen receptor-T cells, most of the new drugs are administered chronically (i.e., up to disease progression or relapse or up to the occurrence of adverse events) aiming to achieve long-term disease control. However, long-term drug administration can result in adverse events and may also increase the risk of interactions with other drugs.

While recognized as a potential risk, the frequency and severity of drug–drug interactions (DDIs) in oncology is not clear. Here, we review current knowledge regarding potential interactions that may involve drugs that have become recently available for patients with lymphoid malignancies and may affect every day clinical practice.

2 | DDIs IN ONCOLOGY

Interactions among concomitantly administered drugs can result in changes in the way one drug acts in the body and thus to altered efficacy or toxicity. DDIs can derive from pharmacokinetic, pharmacodynamic, or pharmaceutical interactions among two drugs (or among a drug and alternative medications, herbs, or food).[9] A pharmacokinetic interaction may affect any of the pharmacokinetic properties (absorption, distribution, metabolism, and/or excretion [ADME]) of one drug by another. The best-characterized is based on cytochrome P450 (CYP) hepatic enzymes and occurs when drugs that reduce (CYP inhibitors) or increase (CYP inducers) CYP activity are concomitantly administered with CYP substrates resulting respectively in decreases or increases in the metabolism of the substrate drug. Interestingly, not only drugs but also food or herbs can have an effect on CYP and therefore interfere with the metabolism of CYP substrates, like grapefruit juice and Seville oranges that can act respectively as strong or moderate CYP3A inhibitors and St. John's wort that can induce CYP3A. Other pharmacokinetic interactions can also occur, including interactions with the P glycoprotein 1 (P-gp) drug transporter that can result in altered drug exposure and finally altered pharmacokinetic properties.[10]

Pharmacodynamic and pharmaceutical interactions occur, respectively, when two drugs have similar mechanism of action (and therefore can result in additive, synergistic, or antagonistic effects) or when there are physical or chemical incompatibilities.[9]

Drug interactions represent an important issue in oncology given the older age of patients with cancer and the frequent use of several medications (so-called polypharmacy) used to treat cancer-related symptoms or concomitant diseases.[11] Older series including mainly patients with solid tumors reported that up to one-third of cancer patients are exposed to potential DDIs.[12] Major potential DDIs were identified in 16% of cancer patients in a large

retrospective cohort[13] and up to 25% of patients on anticancer treatments were found to have a potentially clinically significant DDI in another study performed in one center.[14] A prospective trial including also patients with hematological malignancies, reported potential clinically relevant DDIs in 81 of 302 included patients (27%).[15] Data from patients enrolled in phase II–IV clinical trials with approved medications (mainly tyrosine kinases and monoclonal antibodies) have been also published. DDIs that had to be avoided or drugs to be used with caution were detected by protocol guidance in 10% of patients, although the majority of subjects did not have clinical relevant interactions based on pharmacist review. In the same study, the use of the Lexicomp database detected moderate to major DDIs in 24% of patients with 9.4% having a clinically relevant DDI.[16]

However, despite these data, the real frequency of DDIs in oncology is unclear and there is lack of standardized criteria with regards to clinical consequences and assessment of their severity.[17] For patients with lymphoid malignancies and especially those on treatment with new drugs, data on DDIs are even scarcer. A recent study performed in 118 patients with chronic lymphocytic leukemia (CLL) on treatment with the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib showed that 64% of patients were on medications that could increase ibrutinib toxicity and 3% on medications that could decrease its efficacy.[18]

Over the last years, improvements in our understanding of the biology of lymphomas and advances in antibody technology have permitted the development of many new compounds that have become available for patients with lymphoma and CLL. These new compounds comprise mainly small molecules and monoclonal antibodies which have different mechanisms of action, different toxicities, and potential for DDIs. Taking as a referral Food and Drug Administration approvals of new drugs for lymphomas and CLL over the last 5 years (Table 1), potential interactions, and recommendations for their management will be presented in the following paragraphs.

3 | BTK INHIBITORS

The development of BTK inhibitors has represented one of greatest recent therapeutic achievements in the treatment of lymphoid malignancies. Following the approval of ibrutinib, two other compounds, acalabrutinib and zanubrutinib, have been recently approved, while others are in clinical development and may be added in the list of available therapies for the treatment of lymphoid malignancies responding to BTK inhibitors currently including CLL, mantle-cell lymphoma, marginal lymphoma, and Waldenström's macroglobulinemia.

BTK inhibitors represent a class of compounds with known potential of pharmacokinetic DDIs. The first-in-class inhibitor ibrutinib is primarily metabolized by the cytochrome P450 CYP3A.[19] Although clinical trials in patients with CLL and lymphoma have excluded concomitant use of strong CYP3A inhibitors or inducers, pharmacokinetic studies in healthy volunteers and physiologically based pharmacokinetic models have revealed changes in ibrutinib exposure when administered concomitantly with CYP3A inhibitors or inducers that may be clinically relevant.[20,21] Accordingly, it is recommended to avoid concomitant administration of ibrutinib with strong CYP3A inhibitors or inducers and to consider a reduction of its dose if a moderate CYP3A inhibitor must be used.[22] In addition to the abovementioned CYP3A-mediated interactions which may have a clinical consequence, there is in vitro evidence that ibrutinib may also interact with rituximab antagonizing its antibody-dependent cell-mediated cytotoxicity though inhibition of interleukin-2 inducible tyrosine kinase which is necessary for natural killer cell function.[23] However, the clinical significance of this possible interaction is not known.

Similarly to ibrutinib, the second generation BTK inhibitors acalabrutinib and zunabrutinb are also primarily metabolized by CYP3A, and they have the same recommendation of avoiding coadministration with strong CYP3A inhibitors or inducers. Adaptations of their dose should be considered when CYP3A moderate inducers or inhibitors must be used.[24,25] In addition, acalabrutinib solubility decreases with increasing gastric pH resulting in significant decreases in exposer when administered with antacids and proton-pump inhibitors. Therefore, the recommendation is that acalabrutinb should not be coadministered with proton-pump inhibitors (due to their long-lasting effect), while antacids and H2-receptor antagonists may be administered but at least 2 h after the administration of acalabrutinib.

While the above reported interactions are based on pharmacokinetic mechanism and modulation of CYP3A, there are other potential interactions of BTK inhibitors that should be taken in consideration. In particular, attention should be given to the concomitant administration of anticoagulants which can lead to increased risk of bleeding events. Concomitant administration of warfarin is contraindicated. On the other hand, apixaban and rivaroxaban undergo CYP3A4-mediated metabolism.[26,27]

4 | PHOSPHOINOSITIDE 3-KINASE INHIBITORS

Another class of compounds that have entered clinical development and have beshown activity mainly in CLL and some indolent lymphomas (follicular lymphoma in particular) is represented by phosphoinositide 3-kinase (PI3K) inhibitors. Following the first approval of idelalisib, other compounds targeting PI3K have been developed more recently and two of them, copanlisib and duvelisib, have been approved for follicular lymphoma.

Copanlisib is an intravenous, pan-class I phosphatidylinositol-3-kinase (PI3K inhibitor) with predominant PI3K-α and PI3K-δ inhibitory activity. Approximately more than 90% of copanlisib metabolism is mediated by CYP3A. Strong CYP3A inducers result in significant decreases of copanlisib AUC and Cmax and should not be given concomitantly. On the other hand, CYP3A strong inhibitors cause a significant increase of copanlisib AUC and again should not be

TABLE 1 Selected recently approved drugs for lymphoid malignancies with known CYP3A and/or P-gp interactions. Refer to the prescribing information of each drug.

Drug	Recommendation	Effects on other drugs
Ibrutinib	Avoid concomitant use with strong CYP3A inhibitors. If these inhibitors are used as short-term consider interrupting ibrutinib	May increase the concentration of oral P-gp or BCRP substrates with narrow therapeutic index (e.g. digoxin, methotrexte).
	Dose adjustments (70 mg OD or 140 mg OD) if voriconazole or posaconazole must be given concomitantly	
	Dose adjustment to 280 mg OD if a moderate inhibitor must be administered concomitantly	
	Strong CYP3A inducers should be avoided	
Acalabrutinib	Coadministration with strong CYP3A inhibitors should be avoided or, if the inhibitor will be used short-term, acalabrutinib should be interrupted	Not reported
	Dose adjustment at 100 mg OD if moderate CYP3A inhibitors are used	
	Coadministration with strong CYP3A inducers should be avoided. If they must be used consider increasing the dose of acalabrutinib at 200 mg BID	
	Proton-pump inhibitors should be avoided	
	Antacids and H2-receptor antagonists to be taken at least 2 h after acalabrutnib	
Zanubrutinib	Zanubrutinib dose to be reduced in case of concomitant administration with moderate or strong CYP3A inhibitors	Not reported
	Avoid coadministration with moderate or strong CYP3A inducers	
Copanlisib	Concomitant use with strong CYP3A inhibitors should be avoided. Copanlisib dose to be reduced at 45 mg if a strong CYP3A inhibitor must be used	Not reported
	Strong CYP3A inducers should be avoided	
Duvelisib	Concomitant use with strong CYP3A inhibitors should be avoided. Duvelisib dose to be reduced at 15 mg BID if a strong CYP3A inhibitor must be used	May increase AUC of sensitive CYP3A4 substrates
	Strong CYP3A inducers should be avoided	
Venetoclax	Strong CYP3A inhibitors should not be used during ramp-up. Venetoclax dose to be reduced when strong inhibitors are used at steady state	May increase warfarin Cmax and AUCinf resulting in increased risk of bleeding. Venetoclax increases Cmax and AUCinf of P-gp substrates
	If moderate CYP3A or P-gp inhibitors are used during ramp-up or at steady state, dose of venetoclax must be reduced	
	Concomitant use with strong or moderate CYP3A inducers should be avoided	

Abbreviations: CYP3A, cytochrome P450 3A; P-gp, P glycoprotein 1.

administered concomitantly, or the dose of copanlisib should be reduced in case concomitant use with strong inhibitors cannot be avoided.[28]

Finally, duvelisib, an inhibitor of PI3K with inhibitory activity predominantly against PI3K-δ and PI3K-γ isoforms, is also primary metabolized by CYP3A cytochrome and has the same indications as with copanlisib for strong inducers or inhibitors. In addition, duvelisib can lead to increase AUC of CYP3A substrates and therefore to increased toxicity of these drugs which may require adaptation of their dose.[29]

5 | VENETOCLAX

Another small molecule-targeted agent that has been approved for the treatment of CLL is the bcl-2 inhibitor venetcolax. As with the compounds previously reported, venetoclax is mainly metabolized by the cytochrome CYP3A4.[30] Concomitant use with a strong or moderate CYP3A inhibitor or a P-gp inhibitor increases venetoclax plasma concentration and exposure which may increase the risk of adverse events, including tumor lysis syndrome, a well-known adverse event of venetoclax in CLL and reason for a particular

ramp-up dosing scheme. Therefore, the recommendation is to avoid concomitant use with a strong CYP3A inhibitor at initiation and during the ramp-up phase. During treatment at the steady dose, alternative medications or dose adaptation of venetoclax and frequent monitoring for adverse events should be considered. Strong or moderate CP3A inducers can also result in changes and in particular in decreased exposure to venetoclax and therefore current recommendation is to avoid concomitant administration.

Finally, venetoclax may also alter the exposure to other drugs and in particular it can increase warfarin levels and thus increase the risk of bleeding. International normalized ratio should therefore be regularly checked in patients taking warfarin with venetoclax.

6 | CONCLUSION

Drug interactions can involve recently approved new drugs for patients with lymphoid malignancies. In particular, small molecules-targeted agents are primary metabolized by CAP3A and their coadministration with strong or moderate CYP3A inhibitors or inducers can result respectively in increased or decreased plasma concentrations and therefore in risks of toxicity or decreased efficacy. Awareness of this problem and a regular check of the medications of the patients and consultation with pharmacists in case of any doubts for potential DDIs could help to prevent these interactions and especially those that could result in clinically significant consequences for patients.

CONFLICT OF INTERESTS

Institutional grants for clinical trials: Merck, Bayer, Roche, Novartis, Pfizer, ADC Therapeutics, MEW Pharma, Eli Lilly; advisory board: Roche; consultant: Bayer, Eli Lilly; travel grant: PharmaMar, Abbvie.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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