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Key role of oncopharmacology in therapeutic management, from common to rare cancers

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Summary

The therapeutic management of cancers has undergone considerable changes due to the emergence of genomics tools and tumor molecular deciphering. In this context, a dual pharmacological approach based on pharmacogenomic analyses and therapeutic drug monitoring is now part of the routine care in cancer management for personalized therapies. First, molecular and immune profiling of tumors allows the emergence of new pharmacological targets in common as well as in rare cancers. Second, pharmacogenomic analyses coupled to therapeutic drug monitoring guide the prescription by adjusting regimen and managing drug resistance.

KEYWORDS

Oncopharmacology; Pharmacogenomics; Therapeutic drug monitoring; Targeted therapies; Immunotherapies; Resistance

Abbreviations

ALCL: anaplastic large-cell lymphoma
ALL: acute lymphoblastic leukemia
AML: acute myeloid leukemia
AEs: adverse events
AUC: area under the curve
BRAFi: BRAF inhibitorCAR: chimeric antigen receptor
CML: chronic myeloid leukemia
CTLA4: cytotoxic T-lymphocyte–associated antigen 4
ECD: Erdheim–Chester disease
EGFR: epidermal growth factor receptor
HL: Hodgkin lymphoma
ICIs: immune checkpoint inhibitors
IFN-α: interferon alfa
LCH: Langerhans cell histiocytosis
MAPK: mitogen-activated protein kinase
MEKi: MEK inhibitor
NHLs: non Hodgkin lymphoma
NSCLC: non-small cell lung cancer
PD-1: programmed cell death I
PD-L1: programmed cell death ligand I
PI3K/AKT: phosphoinositide 3-kinase/ protein kinase B
RTK: receptor tyrosine kinases
SCLC: small cell lung cancer
TDM: therapeutic drug monitoring
TKI: tyrosine kinase inhibitor

Introduction

Recent advances in cancer patients have required a new multidisciplinary pharmacological approach in terms of treatment choice, optimization and post marketing authorization surveillance [1]. Genomic tools have considerably changed the treatment of cancers these last years. Based on the characterization of molecular alterations and tumor immune features, targeted therapies and then immunotherapies have greatly improved the clinical course of patients and enlarged the role of pharmacology in cancer therapeutic management. Thus, a dual pharmacological approach relying on therapeutic drug monitoring and pharmacogenomic analyses is now part of the routine care. Indeed, identifying tumor molecular alterations is a key point to guide therapeutic strategies and provide new insights regarding the understanding of drug resistance and the development of response biomarkers.

In this review, we present the contribution of oncopharmacology in patient's management, from common to rare tumor types.

From tumor molecular alterations to pharmacological targets

Genomic and transcriptomic approaches allowed a molecular deciphering of tumors and uncovered alterations in signaling pathways underlining tumor pathogenesis processes. This leads to a better molecular characterization of a wide range of cancers, from common to rare, paving the way for innovative targeted therapies development.

Lung cancer

Lung cancer is a major cause of mortality and the most commonly diagnosed cancer worldwide with 11.6% of the total cases [2]. Comprehensive molecular profiling, notably from the Cancer Genome Atlas research network identified alterations frequently retrieved in the different histological lung subtypes [3].

In adenocarcinoma, the most frequent form of non-small cell lung cancer (NSCLC), the RTK/RAS/RAF signaling pathway is altered in 75% of cases. The major factors leading to this activation are *NF1, KRAS*, *EGFR* and *BRAF* mutations with *EGFR* being the most common driver mutation described in approximately 15% of cases [4]. Based on this molecular characterization,

tyrosine kinase inhibitors (TKIs) targeting EGFR such as erlotinib and gefitinib have greatly improve clinical outcome with an overall response rate of 75% in patients with *EGFR* sensitizing mutations (5). Following the same logic, a combination of dabrafenib (BRAF inhibitor, BRAFi) and trametinib (MEK inhibitor, MEKi) has been approved and showed good clinical benefit in *BRAFV600* mutated (*BRAFV600*^{mut}) patients. Besides the mitogen-activated protein kinase (MAPK) pathway, rearrangements of the *ALK* gene were also uncovered in 3-5% of NSCLC patients prompting to develop successive generations of ALK kinase inhibitors (crizotinib, ceritinib, osimertinib…), which reached an overall response rate of 50 to 60% [6]. Finally, *ROS1* rearrangements uncovered in 2% of patients constitute a good pharmacological target [7,8].

Beyond targeting the driver mutations, efforts regarding the characterization of the tumoral immunologic features and microenvironment have allowed NSCLC to benefit from immunotherapy [9]. Immune checkpoints inhibitors (ICIs) targeting the PD1/PD-L1 interaction (nivolumab, pembrolizumab, durvalumab) or the CTLA4 receptor (ipilimumab) have thus improved the survival compared to molecular targeted therapies and provide innovative therapeutic options for patients not harboring previous molecular alterations [10].

Squamous cell carcinomas which represent approximately 30% of lung cancers are defined by multiple and complex genomic mutations in several pathways, including actionable oncogenic alterations in *FGFR1, PIK3CA, DDR2, MET* and *BRAF* genes [11] constituting opportunities for molecular targeted therapies. Although clinical trials targeting these pathways have failed, ICIs have led to a meaningful increase in response rate and survival [12].

Small cell lung cancer (SCLC) accounts for approximately 15% of lung cancers and is characterized by rapid disease progression. Facing a lack in early detection and a limited amount of tumor tissue for translational research, few is known about its molecular characterization and no targeted therapies are approved for its treatment [13,14]. Currently, mRNA profiling distinguishes two groups according to expression of *CHGA*, *GRP*, *ASCL1* and *DLK1* and co-inactivation of *TP53* and *RB1* are frequent [15]. Besides, several trials evaluating ICIs are ongoing.

Melanoma

Melanoma accounts for approximately 10% of cutaneous cancers and presents a very bad prognosis when diagnosed at an advanced or metastatic stage [16]. Until 2010, cytotoxic chemotherapies such as dacarbazine were the only available treatments for metastatic forms and displayed a poor clinical benefit. Applying whole exome sequencing revealed that melanoma tumors harbor a high rate of

genomic alterations [17] and led to the exhaustive identification of significantly recurrently altered genes. It allowed to establish a molecular classification defining 4 subtypes harboring the following genotypes: (i) *BRAF* kinase mutations; (ii) *NRAS* small G protein mutations; (iii) *NF1* mutations and (iv) triple wild-type , (heterogenous group with no *BRAF*, *RAS* or *NF1* mutations but alterations of *GNAQ, GNA11, KIT* or *CTNNB1* can be retrieved) [18].

Regarding therapeutic management, two major altered signaling pathways were highlighted raising high hopes for the use of molecular therapies: (i) the MAPK pathway activated in more than 75% of melanomas due to *BRAF* (50% of melanomas), *NRAS* or *cKIT* somatic mutations; (ii) The PI3K/AKT pathway with alterations on genes such as *PTEN* or *AKT* [19–21].

Two BRAFi, vemurafenib and dabrafenib, were thus approved to target the constitutive activation of the MAPK pathway successive to *BRAFV600* mutations. Firstly used as a monotherapy, these drugs improve survival in metastatic melanoma patients and a clinical response was observed in 50% of patients [22,23]. Facing multiple treatment escape, BRAFi are now used in combination with MEKi (cobimetinib, trametinib) which is the standard of care in $BRAFV600^{mut}$ metastatic melanoma patients [24,25]. This clinical benefit achieved with BRAFi+MEKi compared to BRAFi alone points out the interest of targeting an altered pathway at different levels to delay escape to therapy. In that extent, trials evaluating the clinical benefit of combining PI3K inhibitors with MAPK inhibitors (MAPKi) are ongoing with promising efficacy data albeit restrained by severe adverse events (AEs) such as stomatitis, creatine kinase increase or cutaneous rash [26,27]. Moreover, alterations of the apoptosis or cell cycle pathways were identified in melanoma, supporting the evaluation of new targeted approach such as CDK4/6 inhibitors [28].

As described in lung cancers subtypes, the characterization of the immune tumoral features has led to the approval of ICIs in metastatic melanoma. Anti-PD1/PD-L1 and anti-CTLA4 immunotherapies thus provide long-term clinical response and are now used as first or second line therapy (after BRAFi+MEKi) in metastatic melanoma patients according to the existence of *BRAFV600* mutation [29–32].

Hematological malignancies

Hematological malignancies concern both adults and children. Tumor mutational profiling of hematological malignancies is significantly different with multiple genomic alterations in elderly patients whereas few targetable mutations have been identified in pediatric patients so far, restraining the development of targeted therapies in this subpopulation [33]. In addition, emerging

evidence shows that immunotherapies are effective against chemo resistant cancer cells when administered alone or in combination with chemotherapy [34].

In chronic myeloid leukemia (CML), TKIs such as imatinib, dasatinib and nilotinib are used and target the oncogenic pathway of Philadelphia (Ph) chromosome (translocation t(9,12)), the main genetic alteration in CML, which results in the BCR-ABL fusion gene. TKIs decrease the induction of proliferation through the ABL-activation [35]. In B-cell acute lymphoblastic leukemia (ALL), blinatumomab, a bi-specific monoclonal antibody mediating the interaction between CD19+ on leukemic blasts and CD3+ on T-cells, is now marketed for the treatment of Ph- recurrent or refractory patients [36]. The induction treatment for children with ALL is a combinatory chemotherapy and the addition of a TKIs, such as imatinib, may be beneficial for Ph+ ALL patients [36]. In acute myeloid leukemia (AML), 85% of children go into remission after chemotherapy induction. However, for relapsing or refractory cases, a promising option besides stem cell transplant or a second cycle of chemotherapy, is the off-label use of gemtuzumab ozogamicin, a monoclonal antibody targeting CD33 [37].

Currently, treatment of Hodgkin lymphoma (HL) is mainly based on the use of chemotherapy and radiation therapy. However, immunotherapy is increasingly used [34,36] and brentuximab vedotin, a conjugate between an anti-CD30 antibody and a cytotoxic agent, is currently approved for use in adults only. ICIs and notably anti-PD1 immunotherapy are labeled for use in adults with refractory or relapsed HL even after stem cell transplant and/or use of brentuximab vedotin. Clinical trials in childhood HL are ongoing.

Treatment of non-Hodgkin lymphomas (NHLs) is mainly based on multi-agent chemotherapy combined or not with local treatments such as surgery and radiation. In patients with CD20+ diffuse large B-cell NHL, rituximab, an anti-CD20 antibody, is indicated in combination with chemotherapies [38].

Treatment with brentuximab vedotin has also been approved to treat relapsed or refractory systemic anaplastic large-cell lymphoma (ALCL) in adults and trials are ongoing in children [39]. Also, the use of ALK inhibitors (crizotinib, ceritinib), alone or in combination with CD4 inhibitors may be more effective in treating children with relapsed or refractory ALCL [40].

Adaptive T-cell therapy has been a breakthrough for the treatment of hematological cancers, especially the development of chimeric antigen receptor (CARs) transgenic T-cells targeting CD19. Use of this therapy in patients with refractory disease to standard chemotherapy has resulted in approximately 66% complete response rate despite short-term toxicity [34]. In children, recent trials demonstrate a 81% overall remission rate within 3 months and no minimal residual disease in responders [41]. Chimeric antigen receptors (CARs) are engineered receptors

that graft a defined specificity onto an immune cell, typically a T-cell, and enhance T-cells function [42]. CARs consist of a T-cell activating domain and an extracellular immunoglobulin-derived heavy and light chains to direct specificity, and second generation CARs also include co-stimulatory domains [43]. Their activation leads to T-cell proliferation, cytokines secretion, and cytolysis. Transgenic CAR T-cells such as CTL019-tisagenlecleucel target the antigen CD19 which can be found on the cell surface of most B-cell derived ALL. Clinical trials evaluating the use of these CAR T-cells have recently showed substantially improved outcomes in patients with refractory B-cell cancers, including NHL, CML and ALL [41,44,45]. Nevertheless, some challenges are inherent to this treatment like short-term AEs, the low levels of long-run persistence of CAR T-cells or the risk of an immune escape [42].

Histiocytic neoplasms

Histiocytic neoplasms are a heterogeneous group of rare clonal hematopoietic diseases with a therapeutic management greatly improved by the genomic approach. For instance, recurrent molecular alterations have been identified in Langerhans cell histiocytosis (LCH) and Erdheim–Chester disease (ECD).

LCH is a rare disease with varying clinical presentations, from localized to severe multivisceral forms [46]. The pulmonary form of the adult occurs selectively in young smokers [47] and tobacco smoking is the only risk factor clearly identified to date [47]. LCH treatment is highly dependent from the clinical presentation [48,49] and surgery, radiation therapy, or chemotherapies have been historically used [49]. In adults, the association vinblastine/prednisone as well as cytarabine or cladribine are usually prescribed [48,50]. In pulmonary LCH, although cladribine may improve lung function [51], vinblastine is ineffective and there is currently no effective treatment [52]. Moreover, these chemotherapies are highly toxic with variable response rate requiring the development of novel therapeutic strategies.

In 2010, the tumoral aspect of the LCH was confirmed and *BRAFV600E* oncogene mutation was identified in approximately half of LCH tissue lesions [53,54]. Recently, wide exome sequencing of LCH lesions revealed other gene alterations in the MAPK pathway, including *BRAF* deletions [55], *MAP2K1* mutations/deletions in about 25% of cases [56–58], as well as *NRAS* [54], *ARAF* [59], *MAP3K1* [58], and *KRAS* mutations [60,61]. These findings highlight that a somatic activating mutation in the MAPK pathway is carried by most LCH patients and support the clinical use of MAPKi. In LCH adults harboring a *BRAFV600* mutation, an overall response rate of 43%

and no disease progression were observed under vemurafenib [62–64]. In children, clinical trials evaluating the safety, the tolerability and the pharmacokinetics of BRAFi are ongoing. MEKi have shown good results *in vitro* [61] and trametinib was effective and well-tolerated in a patient with progressive pulmonary LCH [65]. Overall, MEKi is a relevant therapeutic option as it showed good response in patients with histiocytic neoplasm harboring mutations in *RAF*, *RAS* and *MEK* genes [66]. Moreover, TKIs have emerged as a relevant pharmacological approach and studies have shown the effectiveness of imatinib in the treatment of LCH patients [67,68]. In an open-label multicenter trial, the pan-AKT inhibitor afuresertib provided a clinical stabilization in LCH patients [69]. Despite not targetable, other altered genes such as *ASXL1*, *DNMT3A*, *IDH1*, *TET2* [61,70], *PTPN11* [71] *TP53* and *MET* [53] have also been identified.

Similarly, ECD is a rare non–Langerhans cell histiocytosis (approximately 500 patients diagnosed worldwide since 1930) and no therapeutic trials have been performed so far. Interferon alfa (IFN-α), has long been the first-line therapy [72,73], but the occurrence of severe AEs and the development of secondary resistance to IFN-α high doses [74,75] motivated the investigation of alternative pharmacological strategies. Second-line treatments such as anakinra, cladribine, TKIs and infliximab have been proposed [76] but the small numbers of patients did not allow to define the optimal strategy. Since more than 50% of patients harbor a *BRAFV600E* mutation [77,78], MAPKi may be a relevant therapeutic option and positive outcomes were reported in refractory *BRAFV600E* patients treated with vemurafenib [62]. Other cases reported the efficacy of BRAFi but also MEKi therapy [79,80].

Pharmacogenomic in the management of cancers

Tumor molecular genotyping as part of routine care in France

Drug development and approval for molecularly stratified tumor subgroups have rendered molecular testing mandatory and require that molecular analyses be performed nationwide. To this end, the French National Cancer Institute (INCa) and the French Ministry of Health have set up since 2007, a national network of 28 regional molecular genetics centers working in a multidisciplinary collaboration, involving clinicians, pathologists and molecular biologists. Selective molecular tests are performed in these facilities. They are free of charge for all patients in their region, irrespective of the type of establishment in which they are receiving treatment. An evolutive catalogue of validated molecular predictive biomarkers performed in the INCa platforms

and guiding the prescription of targeted therapies is available. Thus, the genotyping of tumors has become a theranostic tool, which conditions the prescription of targeted therapies. For instance, *EGFR* genotype status will determine the prescription of anti-EGFR targeted therapies in NSCLC and the presence of *BCR-ABL* fusion transcript will condition the use of imatinib, dasatinib or nilotinib in CML. In metastatic melanoma, *BRAF* genotyping is performed for all patients who may benefit from BRAFi. In acral lentiginous and mucosal melanomas c-KIT genotyping will guide a potential treatment with TKIs.

A specific program has also been implemented by INCa to anticipate the launch of new targeted therapies and to accelerate the time-to-access to new drugs and experimental therapies. This initiative has been operational for few years now and has been successful in meeting its initial aims of uniform nationwide test provision and fast implementation of molecular tests for new tumor biomarkers.

Besides these initiatives, INCa implements recommendations regarding molecular tests prescription, genotyping, results and activity reporting.

Management of resistance to therapies

Resistance mechanisms

Multiple resistance mechanisms have emerged and have restrained the clinical benefit of targeted therapies and immunotherapies. In that extent, pharmacogenomic analyses at baseline and under treatment are a key point in therapeutic management allowing the understanding of preexisting and acquired genomic alterations involved in resistance.

Resistance to targeted therapies was firstly documented for imatinib in CML based on mutations in the targeted kinases [81]. In NSCLC, a similar direct oncogene reactivation, due to the activating *EGFRT790M* mutation, was involved in resistance to first-generation TKIs. Successive generations of EGFR inhibitors were hence developed [82]. In metastatic melanoma, multiple resistance mechanisms can bypass BRAF inhibition and acquired resistance occurs in 50% of patients [22,23]. A MAPK pathway reactivation is retrieved in more than 75% of cases [83–87]. Resistance may also be driven by alterations in other oncogenic pathways promoting cell survival and proliferation as well. In NSCLC, resistance to gefitinib through amplification of an alternative

tyrosine kinase receptors such as *MET* was highlighted [88]. In melanoma, the PI3K/AKT pathway may thus be activated through *PTEN* and *AKT* mutations and alterations of cell cycle genes have been associated to resistance [89,90]. Recent studies revealed baseline genomic features predictive of clinical response under MAPKi. For instance, in melanoma, Wongchenko et al. [91] and Yan et al. [92] highlighted improved clinical response in patients carrying baseline *NF1* alterations and higher expression of immune response-related genes. A MAPK pathway activity score predictive of vemurafenib response has been proposed as well [93]. In NSCLC, sensitizing *EGFR* mutations, and *ALK* or *ROS1* rearrangements are known predictive biomarkers of response to targeted therapies and several gene alterations (*KRAS, MET*) are candidates currently studied [94].

Deciphering the efficacy of MAPKi newly prescribed in histiocytic neoplasms, data on resistance mechanisms in this rare disease are beginning to emerge. Recently, a novel *MAP2K1* mutation was related to resistance in a patient treated with trametinib [95]. Similarly, *RASA1* loss was highlighted as a mechanism of resistance to BRAFi treatment which was overcome by adding a MEKi [96].

Resistance to ICIs is reported in 50% of treated patients. As pharmacological activity of immunotherapies relies on T-cells, dysfunction of tumor-specific T-cells drives resistance [97]. *JAK1/JAK2* mutations or alterations of the β-catenin pathway may thus decrease T-cells activity and lead to resistance [98]. Moreover, Hugo et al. identified genes overexpressed in resistance cases and proposed a transcriptomic innate anti-PD1 resistance signature [99]. Other resistance mechanisms described to date include expression of alternative checkpoints (*LAG-3, TIM-3*…) or down-regulation of major histocompatibility complex I [100,101].

A higher TMB was significantly associated with favorable outcome in those patients [102]. Regarding anti-PD1/PD-L1 immunotherapies, PD-L1 expression was also depicted as a promising biomarker of response to anti-PD1 therapy but faced important limitations [103].

Identifying non-invasive biomarkers has raised a lot of interest these last few years and circulating tumor DNA (ctDNA) has been increasingly studied in the field of both molecular therapies and immunotherapies. Many recent data suggest that undetectable or low level of ctDNA at therapy initiation are predictive of increased clinical benefit [104,105].

Overcoming resistance

Many efforts are undertaken to overcome resistance, and several trials are ongoing to evaluate the benefit of combining immunotherapies and targeted therapies to overcome the loss of clinical

benefit. In melanoma, translational data have shown that MAPKi may improve the efficacy of immunotherapy by impacting the tumoral microenvironment. This approach is of great interest as it would allow to synergize the high response rate observed under MAPKi and the long-term clinical benefit provided by ICIs [106,107]. Preliminary results from the phase II TRIDeNT and phase III COMBI-I trials (evaluating respectively dabrafenib+trametinib+nivolumab and dabrafenib+trametinib +spartalizumab) revealed improved response rate [108,109]. Combination of MEKi and anti-PD-L1 is also currently under evaluation in *BRAF* wild-type advanced melanoma but shows less conclusive efficacy.

In NSCLC, the same strategy is experimented with clinical trials testing the combined administration of TKIs and ICIs. For instance, the TATTON phase I trial evaluated the combination of osimertinib and durvalumab. Although efficacy results seemed promising, major AEs occurred [110]. Overall, these data emphasize the therapeutic potential of combining immunotherapies and targeted therapies. Nevertheless, as the effect of targeted therapies on the microenvironment is time-dependent, further studies must be addressed to establish the optimal timing and dosing in this context of combinatory treatments.

Therapeutic drug monitoring in the management of cancers

Besides the genomic approach inherent to these innovative therapies, cancer patient's management requires a careful therapeutic monitoring. Oral administration of molecular targeted therapies has improved the patient's quality of life and treatment efficacy but has also raised concerns regarding fixed doses regimen, drug adherence, and inter-individual pharmacokinetics variability.

Therapeutic drug monitoring (TDM) relies on the quantification and interpretation of drug concentrations in biological fluids considering their metabolic profile, their large inter-individual variability, and the efficacy or AEs exposure relationship. The objectives are to minimize underdosing, prevent from drug resistance, determine the etiology of AEs and monitor dose reductions or interactions in high-risks patients. However, different levels of evidence are retrieved according to the cancer type: it is strongly recommended for common cancers such as blood cancer, recommended in lung cancer or melanoma and remains to be evaluated for rare cancers due to the few pharmacokinetic-pharmacodynamic studies.

General pharmacokinetic characteristics

The main pharmacokinetic characteristics of targeted therapies are summarized in Table 1. The absorption phase of these oral treatments is generally rapid with a plasma peak obtained in 3-6 hours. Food intake significantly increases the bioavailability of lapatinib, nilotinib, bosutinib and vemurafenib, slightly increases the bioavailability of erlotinib and significantly decreases the bioavailability of crizotinib, dabrafenib, dasatinib and sorafenib. Diet has no significant effect on the bioavailability of cobimetinib, and ponatinib. These drugs are widely distributed in tissues and are highly bound to proteins. They are substrates and modulators of efflux transporters (including P-glycoprotein and BCRP) and can therefore interact with the drugs substrates [111]. Moreover, their metabolism is essentially hepatic and mainly involves CYP3A4 cytochrome, which is a source of drug and food interactions. All TKIs are mainly excreted in the stool with a minor fraction excreted in the urine. Renal function therefore has little influence on their pharmacokinetics.

Relationship between exposure and efficacy or adverse events

Lung cancer

Despite no association with response was highlighted [112], higher trough concentrations of erlotinib are significantly associated with an improved progression-free survival and overall survival [113–115]. In addition, cutaneous toxicity of erlotinib was correlated with plasma exposure [115].

Melanoma

A study conducted in 27 melanoma patients indicated that patients with sorafenib plasma exposure (AUCss) greater than 100 µg.h/mL had a better tumor response and greater progression-free survival [116]. Patients with severe AEs (grade 3-4) had a higher plasma exposure (61.9 versus 53 µg.h/mL) [117].

A relationship between tumor progression and vemurafenib plasma exposure was also described with a suggested steady-state pharmacokinetic target of above 42 µg/mL [118–120]. Kramkimel *et al.* also showed a correlation between the increase in vemurafenib plasma concentration and the occurrence of skin AEs of grade >2 in the first 3 months of treatment [120].

Similarly, a study conducted in 27 melanoma patients showed a growing risk of AEs occurrence with dabrafenib trough plasma concentrations [121].

Hematological malignancies

Results from studies in CML patients showed that imatinib trough concentration were significantly higher in patients with a major molecular response and have suggested an imatinib minimum concentration of 1000 ng/mL to achieve a good molecular response [122–124].

A further study conducted in 542 CML patients treated with nilotinib suggested that obtaining the major molecular response after 12 months of follow-up was significantly associated with trough concentration. A correlation between increased plasma exposure (AUC) and corrected QT interval elongation as well as bilirubin elevation was highlighted [125].

Moreover, additional data in CML patients treated with nilotinib uncovered a significant shorter time to reach a major molecular response with residual concentrations >500 ng/mL. This study also correlated plasma exposure with the occurrence of known AEs [126].

Regarding dasatinib, Wang *et al.* showed that the major cytogenetic response was significantly correlated with the residual concentration. Low concentrations were associated with a decreased risk of pleural effusion [127,128].

The use of bosutinib trough concentrations to predict treatment efficacy and occurrence of AEs was raised in a study by Hsyu *et al.* The probability of achieving a complete cytogenetic response at 1 year, a major molecular response and a complete hematologic response increased with bosutinib trough concentrations [129].

Taken together, these data demonstrate the clinical interest of TDM as a complement to genomic analyses in oral molecular targeted therapy management in order to ensure treatment efficacy and safety. Few data are currently available in the field of immunotherapy and future pharmacokinetic-pharmacodynamic evidences would be of great interest in therapeutic management and notably in prediction of severe AEs. In addition, studies conducted on rare cancers such as LCH are missing to date and will be of major importance to improve patient's follow-up.

Conclusion

Tumor molecular deciphering has paved the way for targeted therapy development positioning the pharmacology contribution at the forefront of cancer patients' management. Pharmacogenomics is now complementary to TDM, which provides crucial data for the patient follow-up. As improving therapeutic strategy stratification and overcoming therapeutic resistance will be of major concern in the future, pharmacogenomic analyses will certainly play a pivotal role in treating both common and rare tumor types.

Disclosure of interest

Authors have no competing interest to declare.

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Table 1. Main pharmacokinetic characteristics of targeted therapies.

International non-proprietary name	Metabolic pathway	P-gp		BCRP		T_{max}	$T_{1/2}$	Food effect	CYP3A4 inhibitor effect	CYP3A4 inductor effect
		Substrate	Inhibitor	Substrate	Inhibitor	[h]	[h]			
Lung Cancer										
Ceritinib	CYP3A4	+++	++	x	++	4-6	31-41	Slight increase	+290% AUC +120% C_{max}	-70% AUC -44% C_{max}
Crizotinib	CYP3A4, CYP3A5	+++	+++	x	x	4-6	42	-14% AUC -14% C_{max}	+3,2 x AUC +1,4 x C_{max}	-84% AUC -79% C_{max}
Erlotinib	CYP3A4	+++	+++	+++	+++	4	36,2	Slight increase	+86% AUC +69% C_{max}	-69% AUC
Gefitinib	CYP3A4, CYP2D6	+++	NA	+++	+++			-83% AUC	+80% AUC	
Melanoma										
Cobimetinib	CYP3A4, CYP3A5	+++	x	x	++	2,4	43,6	Negligible	Increased AUC, C_{max}	lower AUC, C_{max}
Dabrafenib	CYP2C8, CYP3A4	+++	NA	+++	NA	2	8	-31% AUC -51% C_{max}	+71% AUC +33% C_{max}	NA
Sorafenib	CYP3A4, UGT1A9	x	NA	+++	NA	3	25-48	-30% AUC	Negligible	-37% AUC
Trametinib	Carboxylesterase	+++	+	x	+	1,5	127	-70% AUC -10% C_{max}	Negligible	Negligible
Vemurafenib	CYP3A4	+++	+	+++	+++	4	51,6	+4,6 x AUC +2,5 x C_{max}	NA	-40% AUC
Blood cancers										
Bosutinib	CYP3A4	x	+++	x	+++	6	34	+170% AUC +180% C_{max}	+ 200% AUC +150% C_{max}	-6% AUC -14% C_{max}
Dasatinib	CYP3A4	+++	+	+++	++	0,5-4	5-6	-14% AUC		-82% AUC
Ibrutinib	CYP3A4	x	++	x	++	1-2	4-13	Increase AUC	+24 x AUC +29 x C_{max}	-90% AUC -92% C_{max}
Idelalisib	Aldehyde oxydase, CYP3A, UGT1A4	++	+	++	+	1-2	8,2	+36% AUC Unchanged C_{max}	+79% AUC +26% C_{max}	-75% AUC
Imatinib	CYP2A4	+++	+++	+++	+++		18	-11% C_{max}	+40% AUC +26% C_{max}	-74% AUC -54% C_{max}
Nilotinib	CYP3A4, CYP2C8	+	+++	+++	+++		17	+82% AUC	+300% AUC	-80% AUC

								+112% C_{max}		-64% C_{max}
Ponatinib	CYP3A4	+++	++	+++	+++	4	22	Negligible	+78% AUC	-64% AUC
									+47% C_{max}	-42% C_{max}

+++: strong substrate or inhibitor; ++: moderate substrate or inhibitor; + : weak substrate or inhibitor; x : neither substrate or inhibitor.

AUC: Area under the curve; BCRP: breast cancer resistance protein; CYP: cytochrome P; h: hours; NA: not available; P-gp: P-glycoprotein; UGT: glucuronosyltransferase.