HHS Public Access

Author manuscript

Basic Clin Pharmacol Toxicol. Author manuscript; available in PMC 2022 January 01.

Published in final edited form as:

Basic Clin Pharmacol Toxicol. 2022 January ; 130(Suppl 1): 23–35. doi:10.1111/bcpt.13623.

Boosting the oral bioavailability of anticancer drugs through intentional drug-drug interactions

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Abstract

Oral anticancer drugs suffer from significant variability in pharmacokinetics and pharmacodynamics partially due to limited bioavailability. The limited bioavailability of anticancer drugs is due to both pharmaceutical limitations and physiological barriers. Pharmacokinetic boosting is a strategy to enhance the oral bioavailability of a therapeutic drug by inhibiting physiological barriers through an intentional drug-drug interaction (DDI). This type of strategy has proven effective across several therapeutic indications including anticancer treatment. Pharmacokinetic boosting could improve anticancer drugs lacking or with otherwise unacceptable oral formulations through logistic, economic, pharmacodynamic, and pharmacokinetic benefits. Despite these benefits, pharmacokinetic boosting strategies could result in unintended DDIs and are only likely to benefit a limited number of targets. Highlighting this concern, pharmacokinetic boosting has mixed results depending on the boosted drug. While pharmacokinetic boosting did not significantly improve certain drugs, it has resulted in the commercial approval of boosted oral formulations for other drugs. Pharmacokinetic boosting to improve oral anticancer therapy is an expanding area of research that is likely to improve treatment options for cancer patients.

Keywords

Pharmacokinetics; Drug-drug interactions; Cancer Chemotherapy; Drug Transporters; Drug Metabolizing Enzymes; Boosting; Anticancer

1 Introduction

While novel anticancer agents were previously almost invariably developed for intravenous use [1], oral anticancer drugs have now dominated the landscape of anticancer drug development for over twenty years [1,2]. Oral administration of anticancer drugs is effective, convenient [2], and preferred by patients [3,4]. The rapid expansion of approved oral anticancer drugs suggests that historical doubts regarding the feasibility of oral anticancer therapy were potentially exaggerated [1]. Together, this supports the development of

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Conflict of Interest Statement

The authors have no conflicts of interest to report.

strategies to improve oral anticancer therapies or facilitate the oral administration of intravenous therapies.

Despite their established efficacy, most oral anticancer drugs suffer from significant limitations including substantial pharmacokinetic (PK) variability that could precipitate adverse events or therapeutic failure [2]. This variability is likely related to the low oral bioavailability of many anticancer drugs [5]. The low oral bioavailability of anticancer drugs is related to both poor physicochemical properties (i.e., chemical stability in gastric and intestinal fluids, aqueous and lipid solubility) and physiological limitations (i.e., first-pass metabolism and efflux transport) [2]. Pharmaceutical and chemical strategies have been developed to overcome poor physicochemical properties (e.g., formulation development to improve dissolution) [2,6]; however, many of these strategies remain in preclinical development and have been reviewed elsewhere [2]. In this mini-review, we focus on strategies that have sought to improve the oral bioavailability of anticancer therapy by reducing physiological limitations including efflux transport or the inhibition of the first-pass metabolism through intentional drug-drug interactions (DDIs). When relevant, we will briefly discuss strategies to improve the physicochemical properties of drugs; however, an exhaustive overview of these strategies is outside the scope of this review.

1.1 Physiologic Barriers Limit the Bioavailability of Anticancer drugs

By definition, a drug's absolute bioavailability (F) is the fraction of the ingested drug that reaches systemic circulation. Absolute bioavailability is the product of the absorbed fraction of drug (F_a), the fraction of drug that reaches the hepatic portal vein unchanged (F_g), and the fraction of the dose that is not metabolized by the liver (F_h).

$$F = F_a * F_g * F_h$$

Whereas physicochemical factors (i.e., dissolution, solubility, or lipophilicity of a drug) are expected to have the largest impact on F_a, physiologic factors are expected to most significantly impact F_g and F_h [2]. The primary physiologic factors impacting the oral bioavailability of most anticancer drugs are drug transporters and drug-metabolizing enzymes. While a complete overview of the individual physiologic mechanisms impacting each oral anticancer drug is outside of the scope of this paper, we will generally describe the drug transporters and enzymes that contribute to the disposition of oral anticancer drugs.

1.1.1 Drug Transporters—Drug transporters facilitate the movement of drugs across the cell membrane. The expression and localization of these transporters impact the bioavailability and systemic distribution of various oral anticancer drugs. Directly impacting bioavailability, transporters may facilitate uptake into or efflux from the intestinal epithelial cells or hepatocytes [7]. While characterizing the interaction between individual transporters and specific drugs is an expanding area of research, the ATP-binding cassette (ABC) superfamily of transporters are expressed throughout the body and impact the bioavailability of many anticancer drugs [8]. The ABC superfamily contains three subfamilies of efflux transporters including P-glycoprotein (P-gp; ABCB1), multidrug resistance-associated protein 2 (MRP2; ABCC2), and the breast cancer resistance protein (BCRP; ABCG2) [8].

P-gp, MRP2, and BCRP are efflux transporters that restrict the absorption of oral anticancer drugs. These transporters serve to remove toxins from the cell and, through this ability, are associated with resistance to anticancer drugs when located on cancer cells [7,8]. These transporters are normally extensively distributed throughout the body, including the luminal side of the intestinal wall, and restrict the uptake of a diverse array of substrates, including many anticancer drugs [8]. Significant intra- and inter-patient variability in the expression levels of these transporters may contribute to variability in bioavailability [7].

1.1.2 Drug Metabolizing Enzymes—The elimination of most orally administered anticancer drugs is primarily mediated by metabolism by drug metabolizing enzymes (DMEs) in the intestine and liver [9]. Metabolism that occurs before the drug reaches systemic circulation (first-pass metabolism) limits bioavailability (i.e., decreases F_g and F_h). Despite a wide variety of metabolic enzymes and pathways, metabolic pathways are often classified as either phase I (e.g., oxidation, reduction, hydrolysis) or phase II (e.g., conjugation) reactions. Phase I reactions are frequently mediated by cytochrome P450 enzymes (CYP). Phase II reactions are facilitated by other enzymes (e.g., UDP-glucuronosyltransferases (UGTs)). Enzymes mediated phase I and phase II reactions are present in both the intestinal wall and liver and contribute to first-pass metabolism [2].

Cytochrome P450 (CYP) enzymes contribute to the phase I metabolism of many oral anticancer drugs [9]. The CYP-superfamily of enzymes is divided into families and subfamilies based on structure; the CYP3A subfamily alone contributes to the metabolism of half of all drugs, including a significant number of oral anticancer drugs (e.g., all of the orally administered tyrosine kinase inhibitors excluding afatinib [6,9]). Expression of CYP3A can vary more than 10-fold in the liver and small intestine donor tissues [10,11]; variable CYP activity could contribute to variability in the bioavailability of oral anticancer drugs.

Nucleoside-derived chemotherapeutics may be metabolized by enzymes responsible for the breakdown of nucleoside bases including dihydro pyrimidine dehydrogenase (DPD), thymidine phosphorylase (TD), and cytidine deaminase (CD). DPD is the rate-limiting enzyme responsible for the first-pass metabolism of fluorouracil (5-FU); variable DPD activity is responsible for the variable and erratic bioavailability of 5-FU [12–14]. TD is involved in the breakdown of purine bases and is responsible for the low bioavailability of trifluridine [15]. CD is highly expressed in the gut and liver and metabolizes the deoxycytidine analog decitabine; when orally administered, decitabine's half-life is limited (<20 minutes) by CD activity [16].

While each independently plays an important role in determining the bioavailability of oral anticancer drugs, there is a significant interplay between the drug metabolizing enzymes and drug transporters. Intestinal efflux transport of parent drug will result in further exposure to drug metabolizing enzymes in the intestine prior to reaching systemic circulation [2]. This interplay may also result in complicated networks of mechanisms determining exposure to an oral drug. For example, intestinal efflux of sorafenib's glucuronidated metabolite into the gut lumen results in recycling back to the parent compound through bacterial glucuronidases [17]. Complicating the mechanistic study of transporter or DME-

regulated DDIs, pharmacologic inhibitors may inhibit both putative drug transporters and metabolizing enzymes [18]. Despite a largely incomplete understanding of potentially complicated underlying mechanisms, several anticancer drugs have low oral bioavailability that is limited by drug metabolizing enzymes and/or drug transporters. Pharmacologic inhibition of these mechanisms could increase bioavailability and improve drug therapy.

2 Intentional Use of Drug-drug Interactions to Increase Bioavailability

A drug-drug interaction (DDI) may occur when one drug (i.e., perpetrator) impacts the metabolism or transport of another drug (i.e., victim). Frequently, DDIs are undesirable (or unanticipated) and will require therapeutic modification (e.g., switching the victim or perpetrator to an alternative drug or adjusting the dose of either drug). However, DDIs may also be used intentionally to improve the PK of a primary drug; PK enhancement, or boosting, uses a boosting drug for the primary purpose of causing an intentional DDI with an agent being used therapeutically. In PK boosting, the perpetrating drug is used to enhance the PK of a separate, therapeutic drug, rather than being used for its therapeutic effects. PK boosting has well-established efficacy in several therapeutic indications including boosting of certain drugs used to treat HIV, Parkinson's disease, or microbial infections [19]. For over 20 years, PK boosting has been used to improve certain HIV drugs by increasing drug exposure and, potentially, altering the distribution and interpatient variability [20]. Similarly, PK boosting of anticancer drugs has potential logistic, economic, pharmacodynamic, and PK benefits.

2.1. Logistic Benefits

PK boosting could facilitate the oral administration of drugs that are otherwise primarily administered intravenously. This shift from intravenous to oral administration could improve quality-of-life for patients; most patients prefer oral anticancer therapy and would prefer to avoid frequent hospitalization and the invasive administration of drugs [3]. Outpatient cancer treatment also conserves hospital resources; the value of this conservation has recently been highlighted by the recent COVID-19 pandemic [21]. Given the established efficacy of currently approved chemotherapeutics and established safety profile of PK boosting agents [22], translation of a boosting strategy to facilitate the oral administration of an approved chemotherapeutic could potentially face less logistic or regulatory hurdles versus comparable pharmaceutical strategies. Moreover, the switch from intravenous to oral administration could result in economic and pharmacodynamic benefits.

2.2. Economic Benefits

PK boosting could decrease the overall cost of chemotherapy. Chemotherapy is the largest cost component of cancer treatment [2]; patients may exhibit poor compliance to anticancer therapy due to the economic burden [23]. PK boosting represents a potential interventional pharmacoeconomic (IVPE) strategy to decrease cost [24]. Facilitating the oral administration of therapeutics conventionally administered IV could reduce hospital visits and provide significant cost-savings [25]. For some intravenous drugs and most drugs that are exclusively commercially available as oral formulations, boosting strategies are expected to decrease the amount of raw drug necessary to be administered orally to achieve the

same drug levels and therapeutic effect associated with the same drug when not boosted. In fact, PK boosting could facilitate 10-fold (or greater) dose decreases for the primary chemotherapeutic [26]. Newer oral therapies are not only significantly more effective than historical therapies (i.e. leading to patients being on the drug longer), but are also significantly more expensive (e.g., $120,000/year for ibrutinib versus historical regimens costing ~$10,000/year) [27]. Administering less raw drug could potentially decrease the total cost of therapy depending on the cost of the PK boosting drug. However, a PK boosted formulation could represent a novel patent opportunity and could conceivably increase the cost of therapy. Given that pharmacoeconomic considerations vary widely over time and between patients, institutions, and countries, intentional DDI strategies seeking to improve oral chemotherapy should likely be developed for reasons beyond potential and/or transient cost decreases. Illustrating this point, other IVPE strategies to mitigate the economic burden of anticancer therapy have been met with obstruction from the manufacturer [24]. Fortunately, the intentional use of DDI to improve chemotherapy is anticipated to result in additional benefits.

2.3. Pharmacodynamic Benefits

PK boosting could provide unique pharmacodynamic benefits. Oral administration allows for more chronic dosing regimens that may result in superior pharmacodynamic effects for certain anticancer therapeutics (e.g., decitabine, topotecan) [2]. Oral administration could decrease the number of patients that are noncompliant or that discontinue treatment early [28]. Furthermore, oral administration could facilitate chronic, “metronomic” dosing regimens resulting in pharmacodynamic benefits (e.g., anti-angiogenesis, activation of immunity) [29,30]. This type of regimen differs from traditional chemotherapy strategies by chronically administering a low dose of chemotherapy rather than administering the maximum tolerated dose (MTD) followed by a period of rest. Additionally, PK boosting could inhibit drug transporters or DMEs that contribute to the resistance of cancer cells and improve the ability to kill cancer cells [7,31,32]. PK boosting could also alter the distribution and improve the exposure of the drug to a therapeutic target (e.g., inhibition of p-gp allows distribution into the brain) [33] or prevent accumulation of a drug in undesirable tissues (e.g., inhibition of transporters to prevent peripheral neuropathy [34]). However, potential alterations in distribution could also result in unexpected toxicities (e.g., CNS side effects) [33]. Similarly, the inhibition of efflux transporters could potentially cause the accumulation of anticancer drugs in undesirable cells; for example, inhibition of efflux transporters on hematopoietic cells may decrease the therapeutic index of certain drugs [35]. Together, potential pharmacodynamic alterations suggest that thorough preclinical characterization is necessary to prevent any unexpected toxicities associated with PK boosting. While clinical investigations of PK boosting to support potential economic and pharmacodynamic benefits are ongoing, empirical evidence from clinical trials supports the ability of PK boosting to improve oral bioavailability and decrease PK variability for some drugs.

2.4. Pharmacokinetic Benefits

PK boosting could increase the oral bioavailability for intravenous drugs that otherwise failed to achieve sufficient drug concentrations when taken orally. Similarly, by increasing oral bioavailability, PK boosting could facilitate the administration of a lower dose of

an anticancer drug with potentially decreased variability in drug levels. As discussed previously, oral anticancer drugs almost universally have significant variability in PK (i.e., drug exposure) as well as pharmacodynamics (i.e., response and adverse events) [2]. Largely based on an established inverse relationship between bioavailability and variability [5], the most widely touted benefit of increasing the bioavailability of oral anticancer drugs is the potential to decrease variability in drug levels [2,6]. Indeed, several clinical trials have demonstrated decreased variability in oral bioavailability with the addition of a PK booster to an oral anticancer drug [26]. However, other clinical trials have noted increased variability [36], even despite increased exposure [37]. Furthermore, whether this decreased variability results in similar or increased efficacy or decreased adverse events remains to be established for most drugs. This could be accomplished, for example, by clinical trials directly comparing the boosted oral regimen to the current standard of care. While these types of studies are being pursued for a few anticancer drugs [38], the boosting of several anticancer drugs remains stalled in early clinical development (e.g., dose-finding), even despite promising results. We will briefly discuss anticancer drugs for which a PK boosting strategy has been pursued (summarized in Table 1).

2.5 Examples of Pharmacokinetic Boosting of Anticancer Drugs

PK boosting has been pursued for a variety of anticancer drugs including drugs otherwise unavailable as oral formulations, drugs with subpar oral formulations, and drugs exclusively available as oral formulations. This strategy is most likely to benefit anticancer drugs with highly variable drug levels, low oral bioavailability mediated by a targetable physiologic pathway, and pharmacodynamic activity primarily mediated by the parent drug. A PK boosting strategy has been pursued for several anticancer drugs that meet these criteria. Notably, while any drug-drug interaction that results in increased exposure of a victim anticancer drug could conceivably be used intentionally, a review of all studied (or conceptual) anticancer DDI is outside the scope of this review; we will discuss examples where PK boosting has explicitly been the intention of the studied intervention. We have searched through PubMed to identify clinical studies with a PK boosting intervention. Presently, we have limited this review to published literature written in English; we have excluded drugs that are not approved to treat cancer. The below list is not necessarily exhaustive, especially given the breadth of this subject (i.e., any DDI could technically be used intentionally). Nonetheless, the below examples are well-characterized and representative of PK boosting strategies that have been tested for anticancer drugs.

2.5.1 Etoposide—Etoposide is a cytotoxic drug used for the treatment of malignancies including small cell lung cancer, germ cell tumors, and lymphomas [37]. Etoposide is most frequently administered intravenously, in part because oral bioavailability is limited and highly variable 47%−76%. Etoposide's oral bioavailability is limited by drug transporters (P-gp, MRP2) [2] and drug metabolizing enzymes (CYP3A4, UGT1A1) [37]. While ketoconazole, an inhibitor of these physiologic mechanisms, reduced the apparent clearance of etoposide and increased the area under the concentration-time curve (AUC) by 20%, this strategy did not decrease variability [37]. Moreover, grapefruit juice, a CYP3A4 inhibitor, decreased bioavailability and did not decrease variability [36]. The inability of pharmacologic modulation to improve etoposide disposition suggests that other factors

contribute more significantly to etoposide's poor bioavailability (e.g., stability in gastric and intestinal fluids [39]); chemical approaches (e.g., development of an etoposide pro-drug) to improve etoposide's bioavailability are potentially more likely to be effective than a boosting strategy [2].

2.5.2 Topotecan—Topotecan is a topoisomerase I inhibitor available for oral or intravenous administration. Topotecan's oral bioavailability is only 40% due to efflux transport, primarily by BCRP [40]. This led to clinical trials combining topotecan with elacridar, a BCRP/P-gp inhibitor. Despite elacridar increasing bioavailability to nearly 100%, variability was only slightly decreased (17% to 11%) [40]. Based on these data, the utility of a PK boosting strategy for topotecan has been questioned [41]; since then, phase 3 clinical trials have noted similar activity between comparable unboosted oral and IV regimens [42].

2.5.3 Taxanes—The taxanes paclitaxel and docetaxel are anticancer drugs primarily clinically administered intravenously to treat a variety of solid tumors. The bioavailability of the taxanes is limited by their poor water solubility, and by intestinal and hepatic transporters (P-gp, MRP2) and DMEs (CYP3A4 (paclitaxel, docetaxel), and CYP2C8 (paclitaxel) [33]. Several approaches to improve taxane bioavailability have been pursued to improve the PK of the taxanes and/or avoid the use of toxic excipients including using drug delivery systems to improve water solubility or by using medicinal chemistry to design taxane pro-drugs or taxanes with lower affinity for P-gp [2]. These pharmaceutical approaches have been successful in some cases; paclitaxel was first approved for oral administration in a lipid formulation by Korea for gastric cancer [43]. Several other pharmaceutical approaches to improve taxane bioavailability are in development [33] including a nanoparticle formulation of docetaxel (CPC634) [44]. These pharmaceutical strategies have complemented boosting strategies using inhibitors of putative drug transporters and DMEs. Boosting strategies have been pursued largely to facilitate the IV to oral switch of the taxanes. Inhibitors of P-gp and/or CYP3A4 have been found to boost the oral bioavailability of paclitaxel and docetaxel [33]. These findings led to promising clinical trials testing the ability of encequidar, a selective P-gp inhibitor, to boost the oral bioavailability of paclitaxel [45] or the ability of ritonavir, an inhibitor of P-gp and CYP3A, to boost the oral bioavailability of solid dispersion formulations of paclitaxel (ModraPac) and docetaxel (ModraDoc) [46,47]; the clinical development of these formulations is ongoing and is likely to result in the eventual commercial approval of an oral, boosted taxane formulation.

2.5.4 Fluorouracil (5-FU)—5-FU is an antimetabolite used in the treatment of several solid tumors. Although 5-FU is available in both intravenous and oral formulations, oral 5-FU has poor and highly variable oral bioavailability due to variable activity of DPD, the enzyme responsible for 5-FU metabolism [12]. Competitive inhibition of DPD activity with gimeracil, uracil, eniluracil or CNDP (3-cyano-2,6-dihydroxypyridine) increases 5-FU bioavailability with decreased interpatient variability [13,14]. Moreover, DPD inhibition reduces the formation of toxic metabolites [2]. Strategies to facilitate the oral administration of 5-FU include using prodrugs (e.g., tegafur, capecitabine) with or without inhibition of

5-FU metabolism (i.e., DPD inhibition) [48]. The combination of a tegafur with boosting agents (uracil (UFT), gimeracil-oteracil (S-1)) has been approved outside the United States (e.g., EMA) to treat a variety of cancers [19].

2.5.5 Trifluridine—Trifluridine is an antimetabolite used in combination with a PK booster to treat metastatic cancer. Unless administered with a PK booster, trifluridine is rapidly metabolized by TD. Trifluridine was initially developed as a novel intravenous fluoropyrimidine like 5-FU; however, initial trials of intravenous trifluridine were disappointing due to the drug's exceptionally short half-life (<30 minutes). Subsequent characterization of trifluridine's oral disposition determined that TD was responsible for extensive first-pass metabolism. Inhibition of TD with tipiracil increased trifluridine AUC by nearly 40-fold; this boost resulted in PK conducive to the treatment of malignancy. Trifluridine combined with tipiracil was approved by the FDA in 2015 [15] and represents an interesting example where pharmacokinetic boosting facilitated the oral administration of a drug that otherwise could not be administered (i.e., intravenously, or orally).

2.5.6 Decitabine—Decitabine is a hypomethylating agent (HMA) used in myelodysplastic syndromes (MDS) and other advanced hematological malignancies ineligible for more intense chemotherapy. Decitabine is rapidly inactivated by the enzyme CDA; this makes decitabine normally unsuitable for oral administration. Treatment with intravenous decitabine is remarkably burdensome and requires parenteral administration for 5–7 days per 28-day cycle, with multiple cycles necessary to achieve a response; an oral formulation could decrease this burden. While the competitive CDA inhibitor tetrahydrouridine (THU) increased decitabine oral bioavailability [16], THU is unstable in acidic environments. This led to the development of cedazuridine, a novel, more stable CDA inhibitor that increases the oral bioavailability of decitabine [16]. A fixed-dose oral combination of decitabine and cedazuridine had equivalent decitabine exposure compared with effective doses of IV decitabine. Clinical trials demonstrated comparable efficacy and safety profiles [38] and led to the FDA approval of the fixed-dose oral combination of decitabine and cedazuridine [16]. Notably, azacitidine, another HMA for similar indications, has recently been FDA and EMA approved for oral use without boosting despite exceptionally low oral bioavailability (17%) [49]. Preclinical data suggests cedazuridine could improve the oral bioavailability of azacitidine [50].

2.5.7 Small Molecule Tyrosine Kinase Inhibitors (smTKI's)—The smTKI's are a rapidly expanding group of orally administered drugs that target signaling pathways important to the survival of the tumor cell. Despite the variable PK of many smTKI's, this group of drugs is invariably administered orally [9]. Thus, the smTKI's lack the logistic benefit of converting an intravenous drug into an oral formulation. Nonetheless, these two groups share several other potential benefits (e.g., economic, decreased variability, pharmacodynamic). While the variable PK of many smTKI's is ostensibly due to low and variable bioavailability [6], there is a lacking number of smTKI's with absolute bioavailability data that is publicly available; absolute bioavailability of the smTKI's is often not determined due to intravenous formulation concerns for drugs with such exceptionally low solubility [6]. Nonetheless, given that the smTKI's are developed for

oral administration, there is somewhat rich data characterizing the physiologic processes that contribute to the disposition of individual smTKI's. Broadly, the disposition of most smTKI's is impacted by poor aqueous solubility [6], CYP3A4, P-gp, and BCRP [9]. Targeting these pathways could improve the low and variable bioavailability of TKI's.

Most smTKI's are characterized by poor aqueous solubility that may be impacted by physiologic factors. Food intake and acid-reducing agents can impact smTKI absorption through altering solubility. Most smTKI's are lipophilic and may be impacted by food intake. Food intake increases the solubility of lipophilic drugs through the fat content of food and subsequent increased bile salt secretion [51]. Food intake results in >2-fold increases in the AUC of certain smTKIs including pazopanib, vemurafenib, and lapatinib. In fact, food intake has been proposed as a cost-saving PK boosting strategy for lapatinib [52]. Interestingly, consistent with nonlinear absorption, simply switching patients from taking pazopanib 800mg once daily to 400mg twice daily increased the minimum concentration (C_{min}) of pazopanib [53]. Conversely, acid-reducing agents may decrease smTKI solubility by elevating the gastrointestinal pH; increased gastrointestinal pH causes several smTKI's to shift towards being unionized. Thus, the bioavailability of some smTKIs is decreased in the presence of acid-reducing agents. Acid-reducing agents decrease the AUC of erlotinib, gefitinib, and pazopanib by ~50% [51]. Despite this observation, administration of an acidic beverage did not significantly increase erlotinib bioavailability at baseline. However, administration of an acidic beverage did increase the relative bioavailability of erlotinib in the presence of an acid-reducing agent [54].

Two case studies have demonstrated that cobicistat, a potent and allegedly selective CYP3A inhibitor [22], could boost drug levels of axitinib and crizotinib respectively [55,56]. Axitinib is an oral multi-kinase inhibitor metabolized by CYP3A that is approved by the FDA and EMA for metastatic renal cell carcinoma (mRCC). In one case study, a patient placed on axitinib had subtherapeutic dose levels despite receiving double the standard dose. Further increasing the dose and adding cobicistat boosted axitinib concentrations; this patient remained on axitinib plus cobicistat for 15 months before progression (versus 8.3 months average survival in this disease state) [55]. Crizotinib is an oral inhibitor of anaplastic lymphoma kinase (ALK) that, similar to axitinib, has substantial interindividual PK variability and is metabolized by CYP3A; patient survival decreases with lower steady-state trough plasma concentrations. A clinical trial was designed to administer cobicistat to patients with low trough levels associated with decreased efficacy. However, the clinical trial was terminated because of the approval of alectinib, a next-generation ALK inhibitor. Nonetheless, in one patient, cobicistat increased crizotinib exposure with no adverse effects [56]. Together, these case studies suggest that cobicistat could boost levels of an oral TKI otherwise unlikely to benefit a patient due to physiologic barriers. However, given that these were case studies (i.e., with limited sample sizes and study designs), these data do not necessarily strongly support the universal adoption of a boosting regimen for these TKIs. However, one clinical trial has explicitly pursued PK boosting of a TKI.

Ibrutinib is an oral TKI targeting Bruton's tyrosine kinase (BTK) that has revolutionized treatment for cancers driven by B-cell proliferation including chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL) [57]. Despite improving survival in these cancers,

ibrutinib has an unfavorable PK profile resulting in some patients having unpredictably higher levels of drug [45] predisposing them to adverse events including diarrhea, neutropenia, musculoskeletal pain, hemorrhage, and atrial fibrillation [57]. The oral administration of ibrutinib suffers from significant interpatient variability in drug exposure likely due to ibrutinib's remarkably low bioavailability (2.7%) [58]. Given that ibrutinib is nearly completely absorbed, the first-pass metabolism through CYP3A is likely responsible for limiting ibrutinib's bioavailability [57]. Supporting this hypothesis, co-administration of ibrutinib with the CYP3A inhibitor ketoconazole increased the dose-normalized AUC of ibrutinib by 24-fold in patients [58]. This led to the design of a clinical trial attempting to boost ibrutinib PK with itraconazole, a strong CYP3A inhibitor that is safer than ketoconazole. This clinical trial found that the addition of itraconazole resulted in a 10-fold increase in ibrutinib exposure with a 2-fold decrease in variability [26]. This clinical trial provides preliminary data supporting the use of PK boosting to improve treatment with ibrutinib.

3 Limitations of Pharmacokinetic Boosting in Cancer

The successful adoption of PK boosting strategies in other disease states (HIV, Parkinson's) and for certain cancer drugs (e.g., 5-FU, decitabine) demonstrates the feasibility of this strategy and the potential benefits of expanding this strategy to other anticancer drugs [19]. However, this strategy is subject to its own limitations and is only likely to benefit a limited number of anticancer drugs; future research is necessary to assess the extent to which PK boosting can benefit individual drugs.

3.1 Unintentional Drug-Drug Interactions

Cancer patients are often treated with multiple medications for cancer, cancer-related conditions, or other concomitant conditions. While inhibition of transporters or DME involved in the disposition of anticancer drugs could boost their PK, these same transporters or DME may be involved in the disposition of other medications. For example, digoxin, a heart medication with a narrow therapeutic index, is a p-gp substrate. Combining a PK boosting drug that inhibits p-gp with digoxin could lead to toxicity. A PK boosting strategy could create an unintentional DDI that results in severe consequences [2,6]. Caution should be exercised in the development of PK boosting strategies to avoid and monitor for unintentional DDI, especially given that the DDI potential of additional medications unrelated to the boosting strategy may not be fully characterized. Together, this concern suggests that the safety and efficacy of a PK boosting strategy will need to be fully characterized before broad adoption. This DDI liability may explain the relative success of boosting strategies that inhibit enzymes that metabolize fewer drugs (e.g., DPD, TD, CDU) versus those that inhibit more promiscuous enzymes (e.g., CYP3A). Nonetheless, CYP3A inhibition strategies have been validated for the treatment of HIV [20] and remain promising to improve the PK of multiple anticancer drugs (e.g., the taxanes). Further mitigating this concern, many oncologists are already exceptionally well-versed in the management of CYP3A-mediated DDIs because cancer patients are frequently prescribed strong CYP3A inhibitors for antifungal prophylaxis. In fact, the use of an antifungal agent

as a pharmacokinetic booster could provide additional pharmacodynamic benefits (i.e., antifungal prophylaxis) beyond those of increasing bioavailability [26].

3.2 Pharmacokinetic Boosting is Only Likely to Benefit Certain Anticancer Drugs

While PK boosting has greatly benefited some anticancer drugs, there are a few drugs that did not significantly improve [39], even despite promising preclinical evidence [41]. As discussed previously, PK boosting is only likely to benefit certain drugs, specifically those with highly variable drug levels, low oral bioavailability mediated by a targetable physiologic pathway, and pharmacodynamic activity primarily mediated by the parent drug with a demonstrated exposure-response relationship. If a drug already has reasonably high oral bioavailability, then it's unlikely that increasing bioavailability will greatly decrease variability, especially if that variability is already low (e.g., topotecan) [41]. Similarly, if a drug's low oral bioavailability is found to be primarily due to pharmaceutical factors (i.e., chemical stability), rather than physiologic processes (i.e., DMEs and drug transporters), then pharmacological targeting of the latter may prove to be ineffective (e.g., etoposide) [39]. If an anticancer drug's therapeutic effects are mediated by active metabolites, then a boosting strategy could negatively impact the therapeutic efficacy of that drug by reducing exposure to those metabolites. Consistent with this idea, a clinical trial investigating PK boosting for crizotinib was terminated and not adapted for alectinib, a next-generation ALK inhibitor, partially because alectinib has an equipotent active metabolite [56]. While newer, more selective, and/or more potent targeted anticancer agents that may not benefit from a PK boosting strategy are welcome additions to the armamentarium of treatment options for malignancies, the rapid expansion of targeted chemotherapeutics could reduce the feasibility of properly developing a PK boosting strategy for older targeted agents. For example, newer BTK inhibitors (acalabrutinib and zanubrutinib) have been approved that may be more effective and less likely than ibrutinib to benefit from a boosting strategy due to higher bioavailability and active metabolites [59]. Thus, to be adopted as the standard of care, pharmacologic boosting of ibrutinib therapy through an intentional DDI interaction would need to demonstrate efficacy greater than or equal to ibrutinib alone and these newer, more selective BTK inhibitors. Future studies are necessary to identify agents likely to benefit from PK boosting or determine if this strategy is effective.

4 Future Directions

While PK boosting strategies are approved for a few anticancer drugs, these strategies largely remain unexplored or in development for most anticancer drugs; the development of boosting strategies requires further preclinical and clinical investigation. The recent development of sophisticated preclinical models with humanized or knocked out DMEs or drug transporters could support investigations determining the relative contributions of physiologic mechanisms limiting the bioavailability of anticancer drugs [60]. These investigations could be used to inform the development of computational models (e.g., physiologically based pharmacokinetic (PBPK) models) to determine the relative contribution of physiologic barriers to a drug's disposition. These models could be used to select a dose of a drug that, when combined with a pharmacologic inhibitor, achieves exposure similar to that of therapeutic doses of the drug alone [61]. Well-designed

preclinical studies demonstrating the mechanisms underlying a drug's low bioavailability and the ability of pharmacologic inhibitors to increase exposure through that mechanism could inform the design of clinical trials testing this strategy.

Clinical trials demonstrating a benefit over conventional therapy will be critical to the adoption of a CYP3A boosting strategy to improve oral anticancer therapy. While several of the studies reviewed presently provide proof-of-concept [26] or individual cases where this strategy was used to individualize anticancer therapy [55,56], only a few drugs have data supporting the commercial approval of boosted formulations [16,62]. For other drugs to adopt PK boosting strategies, future clinical studies would ideally demonstrate that a boosted dose of an oral anticancer therapy achieves outcomes more desirable than the conventional use of that drug (e.g., decreased adverse events or therapeutic failure). Based on the previously discussed limitations associated with this type of strategy, fully developing potential PK boosting strategies through phase I, II, and III clinical trials is most appropriate to ensure that a PK boosting strategy is effective and does not cause adverse events.

To validate the results from such studies, sophisticated PK and pharmacodynamic assessments would ideally demonstrate superior outcomes (e.g., decreased variability in drug levels) with the boosted drug despite exposure similar to that attained with higher doses of the drug alone or, when appropriate, exposure similar to that attained with a conventionally used intravenous formulation. This type of PK and pharmacodynamic monitoring of individual patients would closely resemble therapeutic drug monitoring (TDM), a strategy that seeks to decrease interindividual variability in drug responses by altering drug doses depending on PK or pharmacodynamic parameters. Indeed, the adoption of TDM could complement a PK boosting strategy. For example, TDM could identify patients with low drug levels that require PK boosting at baseline with standard doses of chemotherapy (as was intended to be tested with crizotinib [56]). However, while TDM could allow the identification of any patients that respond abnormally to a PK boosting strategy and facilitate the modification of their dose, there are logistical challenges to the adoption of TDM [63] and lacking evidence supporting the widespread adoption of TDM strategies for targeted therapies [64]. Nonetheless, PK and pharmacodynamic analyses will be important to the assessment of PK boosting strategies; these analyses could feasibly be used to support a strategy combining PK boosting with TDM.

5 Conclusions

In conclusion, oral anticancer drugs are effective and convenient for patients. PK boosting is a promising strategy that increases drug levels by inhibiting physiologic barriers; this strategy could improve certain anticancer drugs through potential logistic, economic, pharmacodynamic, and pharmacokinetic benefits. This strategy has transformed treatment with several anticancer drugs by allowing for the oral administration of drugs that would otherwise necessitate intravenous administration. Despite these successes, PK boosting is associated with risks and is only appropriate for a limited number of targets. To mitigate the potential risks associated with this strategy, the impact of PK boosting strategies on both PK and pharmacodynamics should be fully characterized. Ongoing and future investigations will

provide this information and allow for the continued development of strategies seeking to improve anticancer drugs through PK boosting.

Acknowledgements

The work was supported in part by the National Institutes of Health Grants R01CA215802 (to A.S.), R01CA138744 (to S.D.B.) and F31CA254151 (to E.D.E.), by the OSU Comprehensive Cancer Center Pelotonia foundation (A.S. and S.D.B.) and by the Pelotonia Fellowship Program (E.D.E.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies.

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Table 1.

Examples of Pharmacokinetic Boosting of Anticancer Drugs

Therapeutic Drug	Boosting Agent	Suggested Mechanism	Impact of Boosting on Bioavailability	Impact of Boosting on Variability	Latest Phase of Clinical Development	Ref
Etoposide	Ketoconazole	P-gp UGT1A1 CYP3A4	20% increase in AUC	Increased from 43% to 89%	I	[37]
Etoposide	Grapefruit Juice	P-gp CYP3A4	26% decrease in AUC	Increased from 38% to 53%	I	[36]
Topotecan	Elacridar (GF120918)	P-gp BCRP	Increased oral bioavailability from 40% to 97%	Decreased from 17% to 11%	I	[40]
Paclitaxel[a]	Cyclosporin	P-gp CYP3A4	Increased oral bioavailability from <10% to 28%	Remained ~50%	I	[65]
Paclitaxel[a]	Ritonavir	P-gp CYP3A4	Unclear; Paclitaxel exposure is similar when given with ritonavir or cyclosporin	Unclear	II	[47,66]
Paclitaxel[a]	Elacridar (GF120918)	P-gp BCRP	Increased oral bioavailability from <10% to 50%	Remained ~50%	I	[67]
Paclitaxel[a]	Encequidar (HM30181A)	P-gp	Unclear, but bioequivalent to single dose of IV paclitaxel 80mg/m^2	Unclear	III	[45]
Docetaxel	Cyclosporin	P-gp CYP3A4	Increased oral bioavailability from 8% to 90%	Decreased from 90% to 67%	I	[68]
Docetaxel	Ritonavir	P-gp CYP3A4	Increased oral bioavailability from <10% to 161%↑	Decreased from ~90% to 44% – 70%	II	[46,69]
Docetaxel (Oradoxel)	Encequidar (HM30181A)	P-gp	Ongoing	Ongoing	I	[70][b]
Docetaxel	ONT-093	P-gp	Increased oral bioavailability from <10% to 26%	Decreased from ~90% to 31%	I	[71]
1-ethoxymethyl derivative of 5-FU	CNDP	DPD	Increased AUC	Decreased	II	[72]
5-FU	Eniluracil	DPD	Bioavailability of 5-FU is increased to virtually 100%, increased half-life by 20-fold, decreased clearance by 20-fold	Decreased to 20%	II	[73,74]
5-FU (Tegafur)	Uracil	DPD	Comparable levels of 5-FU in normal tissues and plasma, but 5- to 10-fold greater concentrations of 5-FU in tumor tissues	Remained ~50%	Approved (MHLW)	[75,76]
5-FU (Tegafur)	Gimeracil/ Oteracil	DPD	Increased AUC by 6-fold	Decreased to 35%	Approved (EMA, MHLW)	[74]
Trifluridine	Tipiracil	TD	Increased AUC by 38-fold	Unclear	Approved (FDA, EMA, MHLW)	[77]
Decitabine	Cedazuridine	CD	Unclear, but bioequivalent to single dose of IV decitabine 20mg/m^2	Unclear	Approved (FDA, EMA)	[38]
Axitinib	Cobicistat	CYP3A	Case Study[b]	Case Study[b]	Case Study[b]	[55]
Crizotinib	Cobicistat	CYP3A	Case Study[b]	Case Study[b]	Case Study[b]	[56]
Ibrutinib	Itraconazole	CYP3A	Increased dose-adjusted AUC 10-fold	Decreased from 104% to 55%	I	[26]

[a] Intravenous paclitaxel exhibits nonlinear pharmacokinetics due to Cremophor EL, a co-solvent, that is not absorbed orally. While each of these inhibitors increases exposure to oral paclitaxel, it is more complicated to interpret the impact of each of these inhibitors on paclitaxel's bioavailability/variability [2].

[b] Case study unable to determine impact on bioavailability and variability