Combination of small-molecule kinase inhibitors and irinotecan in cancer clinical trials: efficacy and safety considerations

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Background: The combination of small-molecule kinase inhibitors (KI) and the cytotoxic chemotherapy drug irinotecan, albeit studied extensively in both pre-clinical and clinical studies, has not been adopted in clinical practice. We describe the available evidence regarding the efficacy and safety of the combination of KI/irinotecan and explore the possible reasons for its failure to be translated into clinical practice.

Methods: Relevant *in vitro* and *in vivo* studies were identified from Medline and abstracts of the American Society of Clinical Oncology (ASCO) annual meetings published from inception until June 2017. The results of studies for the combination of irinotecan and KI in cell lines, animal models and human trials are summarized.

Results: The majority of KIs exhibit synergistic activity with irinotecan in tumour cell lines. However, published phase I/II clinical trials in cancer patients failed to show good tolerability due to the overlapping toxicity of the combination, particularly diarrhoea and neutropenia. KIs influence the metabolism of the active metabolite SN-38 [through UDP-glucuronosyl transferase 1A1 (UGT1A1) inhibition and impaired transport] resulting in increased exposure and toxicity related to irinotecan.

Conclusions: Despite improved tumour cell death, the clinical use of the combination of KIs and irinotecan is limited by significant toxicity. Caution is recommended especially with dosing and scheduling of the regimen when planning future clinical trials. The need for thorough pre-clinical evaluation of the effects of KIs on UDP- glucuronosyl transferase (UGT) enzymes and transporters before human trials cannot be over-emphasised.

Keywords: Axitinib; cabozantinib; erlotinib; gefitinib; lapatinib; pazopanib; regorafenib; sorafenib; sunitinib; vandetanib; irinotecan; SN-38

Introduction

Irinotecan (CPI-11), a camptothecin analogue and topoisomerase I inhibitor, is an important cytotoxic drug used in the treatment of advanced colorectal cancer (1). It has significant activity against other cancers including small cell lung cancer, gastric cancers and gliomas, making it one of the most commonly used anti-cancer drugs in clinical practice and be listed in the World Health Organization's model list of essential medicines (2-5). Irinotecan is associated with significant, but, unpredictable myelosuppression and diarrhoea as major dose-limiting toxicities. The incidence of severe diarrhoea and neutropenia in irinotecan containing regimen has been reported up to 40% in published trials (6). Such risk for adverse effects is partly attributable to its complex

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pharmacology (7). Moreover, pharmacogenetic testing for UGT1A1 based dosing has been recommended to reduce irinotecan related toxicity (8).

Irinotecan is a prodrug that is activated by carboxylesterases (CES) in the blood circulation and tumour cells to its active metabolite, SN-38 (7-ethyl-10-hydroxycamptothecin), which is 10–1,000 fold more active than the parent compound (9). Glucuronidation of SN-38 to form SN-38 glucuronide (SN-38G) by UGT1A1 results in its inactivation and facilitates elimination. Other enzymes, notably UGT1A7, UGT1A9 and cytochrome P450 3A4/5 (CYP3A4/5) may also contribute to SN-38 metabolism in liver, gastrointestinal tract and kidney (10). Enterohepatic cycling of SN-38G is known to be associated with delayed diarrhoea, a common toxicity in irinotecan treated patients (11). Moreover, various transporters (SLCO1B1, ABCB1, ABCC1 and 2, and ABCG2) are also involved in the clearance of irinotecan and SN-38 (12). Polymorphic variants of UGTs and transporters lead to high inter-individual variability in pharmacokinetics (13,14) .

In current clinical practice, irinotecan is administered either alone or in combination with other cytotoxic drugs such as 5-fluorouracil or capecitabine. In addition, it has been safely and effectively combined with various targeted agents such as monoclonal antibodies (15)—bevacizumab, cetuximab or panitumumab, but, not with the small-molecule kinase inhibitors (KIs). Many KIs have been approved since 2001 to treat various malignancies, either as monotherapy or in combination with chemotherapy drugs (16). Despite synergistic activities for the combination of a KI with irinotecan, none of the KIs are currently used with irinotecan in clinical practice. Possible reasons include overlapping toxicity, drug-drug interactions and lack of efficacy in human trials.

In this review, we summarize the available evidence on the *in vitro* and *in vivo* studies addressing the effects of the combination of irinotecan with the approved KIs. We focused on the anti-vascular endothelial growth factor (VEGF) pathway inhibitors (axitinib, pazopanib, regorafenib, sorafenib, sunitinib), and epidermal growth factor (EGF) pathway inhibitors (erlotinib, gefitinib, lapatinib). These two groups of KIs have been commonly evaluated in combination with irinotecan in the treatment of various cancers. We further summarize the effects of these KIs on the *in vivo* metabolism of irinotecan/SN-38. Finally, we address the potential pitfalls to avoid while planning future studies that address the feasibility of combining a KI with irinotecan.

Methods

We identified the relevant *in vitro* and *in vivo* studies from Medline and abstracts of the American Society of Clinical Oncology annual meetings published from inception until June 2017. The following search terms were used for the literature search—axitinib, cabozantinib, erlotinib, gefitinib, lapatinib, pazopanib, regorafenib, sorafenib, sunitinib, vandetanib, irinotecan and SN-38. Data on pharmacodynamic and pharmacokinetic (PK) interactions between the KIs and irinotecan were extracted from studies published in full or abstract only in English language and summarized in cell lines, animal models and human clinical trials.

Results

Pharmacodynamic interactions

Pre-clinical studies—cell lines and xenografts

Most of the KIs showed synergistic activities when used in combination with irinotecan or SN-38 in cell line studies or xenografts in animal models. Tumour cell apoptosis, cell proliferation, reduction in tumour size and survival of the animals were the common outcomes assessed in these studies. One common theme from these studies confirmed a schedule-dependent interaction between KIs and irinotecan. For example, concurrent administration of gefitinib and irinotecan resulted in an antagonistic effect in two different lung cancer cell lines (PC-9 and PC-9/ZD cells) (17) while sequential administration of gefitinib after irinotecan resulted in potent inhibition of various cell lines (18). Studies addressing the mechanism responsible for synergism identified that KIs caused inhibition of efflux ATP-binding cassette (ABC) transporters (ABCB1 and/or ABCG2) within tumour cells thereby increasing the intra-tumoral concentration of irinotecan and SN-38. Another potential mechanism is inhibition of intra-tumoral UGT1A enzymes by the KIs (19).

In vitro cell line studies evaluating the combination of irinotecan/SN-38 and KIs

Gefitinib exhibited synergistic activities with irinotecan (20-22). In gastric cancer cell lines (19), decreased expression of UGT1A1 and ABCG2 was detected when the combination was tested. Lapatinib restored sensitivity to SN-38 in small cell cancer cell lines through ABCB1 inhibition (23), and potentiated the activity of irinotecan in colorectal cancer cell lines (24). Similarly to gefitinib, lapatinib decreased expression of UGT1A1 and ABCG2 in gastric cancer cell

lines (19). Moreover, erlotinib (25), gefitinib (26), and lapatinib (27) inhibited ABCG2 mediated resistance to irinotecan in cell lines by reducing the efflux of SN-38.

Among the VEGF pathway inhibitors, most KIs had synergistic activity with irinotecan; axitinib demonstrated activity in pancreatic cancers (28), sunitinib in esophagogastric and paediatric brain tumours (29,30), and sorafenib in colorectal cancer (31) and paediatric brain tumours (30).

Animal models

Few animal studies were identified evaluating the combination of KIs and irinotecan. Erlotinib (32) (in LoVo colon cancer models) and lapatinib (in her-2 positive small cell cancer mice models as well as in xenografts) increased tumour cell kill when used with SN-38 (23,24). Vandetanib was synergistic with irinotecan as well as radiation in tumour xenografts (33,34).

PK interactions

Irinotecan metabolism is well characterised. UGT1A1-mediated conversion of the active SN-38 to SN-38G is the primary clearance mechanism (10). As described previously, other enzymes such as UGT1A7, UGT1A9 and CYP3A4/5 and the transporters SLCO1B1, ABCB1, ABCC1 and 2, and ABCG2 play a role in the elimination and distribution of irinotecan and SN-38 (12). Clinically available KIs are known to be substrates, inhibitors and/or inducers of CYP, UGT enzymes and transporters (35-37), indicating a significant potential for drug-drug interactions when used with irinotecan.

In vitro studies on the effects of KIs on SN-38 metabolism by UGT1A1

Many KIs inhibit UGT1A1, although the potency of inhibition differs between the individual agents. Notably, sorafenib and regorafenib are the most potent inhibitors of UGT1A1 identified to date. Sorafenib and regorafenib inhibited the human liver microsomal (HLM) glucuronidation of the prototypic UGT1A1 substrate β-estradiol, with K_i values of 33 and 20 nM, respectively (38). Lesser inhibition was observed with lapatinib and pazopanib; K_i values ranged from 567 to 2,340 nM. The potent inhibition observed with sorafenib and regorafenib accords well with the hyperbilirubinemia (arising from inhibition of UGT1A1-catalysed bilirubin glucuronidation) reported as an adverse effect in patients treated with these drugs, and it would be anticipated that sorafenib and regorafenib would similarly inhibit the glucuronidation of other UGT1A1 substrates (38). Not un-expectantly, sorafenib has been reported to inhibit human liver microsomal SN-38 glucuronidation (K_i—2.7 μM) (39). The Ki for sorafenib inhibition of SN-38 glucuronidation is almost certainly over-estimated, probably by an order of magnitude, due to the failure to account for the non-specific binding of sorafenib to the enzyme source in the *in vitro* incubation medium. Indeed, as discussed subsequently, co-administration of sorafenib and irinotecan leads to an increase in the AUC of SN-38. It is additionally possible that sorafenib and sorafenib glucuronide contribute to the impairment in SN-38 elimination via inhibition of SLCO1B transporters (40) (see below).

It has similarly been reported that erlotinib, gefitinib, lapatinib and sunitinib variably inhibit the *in vitro* glucuronidation of SN-38. Erlotinib was found to be a potent non-competitive inhibitor of SN-38 glucuronidation in pooled HLMs (K_i of 0.68±0.04 μM) and recombinant UGT1A1 (0.81±0.05 μM) (41). An increase in the area under the curve (AUC) of 24–46% for irinotecan was predicted when used with erlotinib (42). The polymorphic variant, UGT1A1*28, was also inhibited by erlotinib (42). Fujita et al reported IC_{50} values for KI inhibition of SN-38 glucuronidation for other KIs— lapatinib (1.47 μM), and gefitinib (3.50 μM) while sunitinib did not inhibit glucuronidation at clinically relevant concentrations (>10 μM) (43).

In vitro studies on the effects of KIs on Irinotecan/ SN-38 metabolism by CYP enzymes

CYP enzymes play a relatively minor role in the metabolism of irinotecan. There has been only a single study that evaluated the effect of a KI on CYP mediated metabolism of irinotecan (44). Gefitinib inhibited HLM CYP3A4 catalyzed formation of NPC [7-ethyl-10-(4-amino-1-piperidino) carbonyloxycamptothecin] (2.8 folds) while it stimulated the formation of APC {7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino] carbonyloxycamptothecin} (1.9 folds) (44). This interaction was considered unlikely to be of clinical relevance.

In vitro studies on the effects of KIs on Irinotecan/ SN-38 transport

Irinotecan and SN-38 are substrates of the ABC transporters ABCB1, ABCC2, ABCG2, whereas SN-38 is a substrate of SLCO1B1 (12). Most KIs appear to be either substrates and/ or inhibitors of ABC transporters (45-47). Among the several KIs evaluated by Zimmerman et al,

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most of the anti-VEGF inhibitors including sorafenib, pazopanib, sunitinib and vandetanib were substrates of SLCO1B1 and SLCO1B3 (40). However, the inhibition of SLCO1B1 by KIs is not well characterised except for pazopanib (IC_{50} of 0.79 μM) (48). Thus, the concentrations of irinotecan and SN-38 in the plasma, gut lumen and within tumour cells could potentially be increased by KI inhibition of transporters. While this complex interplay between KIs and irinotecan results in increased efficacy of irinotecan (in terms of tumour cell kill), there is a simultaneous increase in toxicity (neutropenia and diarrhoea from high concentrations of SN-38 in plasma and gut lumen respectively). This was confirmed for gefitinib *in vivo* studies where an increased bioavailability of SN-38 was seen in rats and mice (49,50).

KI and irinotecan combination in human clinical trials

A substantial number of phase I and II trials evaluating the safety and efficacy of the combination of a KI with irinotecan in cancer patients have been published (*Table 1*). There were no phase III studies assessing the KI and irinotecan combination, except for one trial that was prematurely stopped due to futility (68). The identified studies included both paediatric and adult population with different types of cancers. Gefitinib and sunitinib were tested in six different combination studies each while, sorafenib in four, erlotinib and vandetanib in two each, axitinib, lapatinib pazopanib, and regorafenib in one each trial. Several irinotecan based regimens were used in clinical trials. Irinotecan was either given as monotherapy or as poly-chemotherapy regimen with folinic acid and 5 fluorouracil as FOLFIRI and/or monoclonal antibodies such as bevacizumab and cetuximab.

The individual doses of KI or irinotecan in the combination varied across trials. As expected, most trials had dose escalation strategies with lower starting doses of the KIs or irinotecan. A consistent theme from the trials was that the maximum tolerated dose (MTD) was lower than either drug alone (*Table 1*). For example, the MTD of sorafenib was 200 mg twice daily (a 50% reduction in dose compared to monotherapy) for 8 days out of the 14-day cycle when combined with FOLFIRI and bevacizumab in the Hubbard *et al.* trial (59). Similarly, the dose of sunitinib in combination with FOLFIRI was 37.5 mg daily for 4 out of 6 weeks which is 75% of the usual monotherapy dose (68,69).

On the contrary, none of the trials demonstrated

increased efficacy when the KI was combined with irinotecan based chemotherapy regimen. The combination was highly toxic with an increased incidence of grade 3 or 4 toxicities especially neutropenia (range, 5–96%) and diarrhoea (range, 4–100%). Sunitinib combination studies were particularly toxic with very high incidence of diarrhoea and neutropenia (69,71,72).

PK assessment confirmed an increase in AUC, bioavailability and decreased clearance for irinotecan and SN-38 when co-administered with different KIs (*Table 1*). Majority of the KIs affect AUC (range, 16–100% increase) or clearance of SN-38 (range, 10–600% decrease). However, irinotecan or SN-38 induced increase in the plasma concentration of the KIs was uncommon. For example, there was 50% increase in the AUC of gefitinib when given with irinotecan (55). Such bi-directional changes in PK parameters suggest a complex drug-drug interaction involving transporter-metabolism interplay.

Discussion

Historically, combination cytotoxic chemotherapy regimens have resulted in the cure of various malignancies such as germ cell tumours, lymphomas and leukemias. Such combinations were developed empirically when pre-clinical and clinical studies showed synergistic activity with minimal overlapping toxicity (76). Recent advances in the understanding of the molecular underpinnings of cancer have led to the development of many targeted agents such as monoclonal antibodies and KIs that has improved survival outcomes of hard-to-treat cancers including melanoma, renal cell cancers and thyroid cancers (16). However, resistance to targeted agents is common with treatment. One approach to prevent resistance is by combination therapy with one or more cytotoxic chemotherapy drugs.

There is evidence demonstrating that combination therapy with cytotoxic chemotherapy and targeted drugs has proved to be effective for certain cancers. The combination of cytotoxic drugs with monoclonal antibodies has markedly improved outcomes of cancers, particularly non-Hodgkin's lymphomas, breast, colorectal, head/neck cancers and cervical cancers (77). However, the combination of KIs with chemotherapy drugs has been shown to be ineffective and/or poorly tolerated in clinical trials. Lapatinib with capecitabine for her-2 positive breast cancers and erlotinib with gemcitabine for pancreatic cancers are the only exceptions approved for clinical practice (78,79). The failure of most trials that combine a KI with chemotherapy

Table 1 Human clinical trials with KIs and irinotecan

Drug	Combination	Outcomes	Toxicity	
			Neutropenia	Diarrhoea
Gefitinib				
Horiike *et al*. (51); phase I	Gefitinib 250 mg; irinotecan 50–150 mg/m^2	MTD was not reached	37%	15%
Furman *et al*. (52); phase II	Two courses of irinotecan [15 mg/m^2/day (daily ×5)] were combined with 12 daily doses of gefitinib (112.5 mg/m^2/day)	N/R	N/R	40%
Furman *et al*. (53)	As above PK study with one oral dose of irinotecan	Bioavailability of irinotecan increased by 4 folds; 2-fold decrease in Clearance; SN-38—Clearance decreased by 6 times; ↑bioavailability	N/R	N/R
Sontoro *et al*. (54); phase II randomized	FOLFIRI vs. FOLFIRI/gefitinib	No difference in outcomes between the two arms	35.3%	33.3%
Chau *et al*. (55); phase I/II	Irinotecan 225 mg/m^2 3 weekly with gefitinib 250 mg/day	50% ↑gefitinib AUC; no effect on irinotecan	15.4%	35.9%
Meyerhardt *et al*. (56); phase I	Gefitinib + IFL	MTD gefitinib 250 mg/day, irinotecan 100 mg/m^2, bolus 5-FU 400 mg/m^2, and leucovorin 20 mg/m^2	20.8%	16.6%
Veronese *et al* (57); phase II	Gefitinib + FOLFIRI	Gefitinib 250 mg; Irinotecan dose reduced	62%	54%
Sorafenib				
Azad *et al*. (58); phase I	Sorafenib + cetuximab + irinotecan	RP2D was irinotecan 100 mg/m^2 i.v. days 1, 8; cetuximab 400 mg/m^2 i.v. days 1 and 250 mg/m^2 i.v. weekly; and sorafenib 400 mg orally twice daily	11%	17%
Mross (39); phase I	Sorafenib + irinotecan	Sorafenib 400 mg twice daily + irinotecan 125 mg/m^2 or 140 mg/m^2. 120% ↑—AUC SN-38. AUC— sorafenib ↑68%	5%	40%
Hubbard *et al*. (59); phase I	Sorafenib + FOLFIRI + bevacizumab	MTD for sorafenib—200 mg twice daily on days 3–6 and 10–13 of each cycle; rest—standard doses	47% grade 3 or 4	35% grade 3 and 4
Samalin *et al*. (60); phase I	Sorafenib + irinotecan	MTD of irinotecan 180 mg/m^2 every 2 weeks; sorafenib 400 mg bid	37% grade 3	35% grade 3 and 4
Axitinib				
Bendell *et al*. (61)	Axitinib + FOLFIRI	Axitinib 5 mg bid + FOLFIRI	NR	28%
Pazopanib				
Deslandes *et al*. (62)	Pazopanib + cetuximab + irinotecan	MTD—250 mg/m^2 weekly Cetuximab, 150 mg/m^2 biweekly Irinotecan + 400 mg daily pazopanib; Cmax—irinotecan ↑16%; no effect on SN-38	30% grade 4	5%

Table 1 (*continued*)

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Table 1 (*continued*)

Drug	Combination	Outcomes	Toxicity	
			Neutropenia	Diarrhoea
Bajetta (63) *et al*.; phase I	MTD	RP2D: erlotinib 100 mg per day, irinotecan 180 mg/m^2 and capecitabine 1,500 mg/m^2 per day for 14 days	66%	4/9
Messersmith *et al*. (64) ; phase I	FOLFIRI + erlotinib. No PK effect; stopped after six patients	100 mg/day erlotinib and dose-reduced FOLFIRI (150 mg/m^2 i.v. day 1 irinotecan, 200 mg/m^2 i.v. folinic acid, 320 mg/m^2 i.v. bolus days 1 to 2 5-FU, and 480 mg/m^2 i.v. 5-FU infusion over 22 hours, days 1 to 2)	50%	50%
Lapatinib				
Midgley *et al*. (65); phase I	Lapatinib FOLFIRI 108 mg/m^2 40% dose reduction of 5-FU & irinotecan	41% ↑ in AUC—SN-38	77%	23%
Regorafenib				
Schultheis *et al*. (66); phase I	Regorafenib 160 mg/day 4–10 + FOLFIRI	AUC: 28%↑ for irinotecan. SN-38—44% ↑	45% grade 3 or 4	10% grade 3 or 4
Ma *et al*. (67); phase I	Regorafenib 120 mg/day + FOLFIRI—irinotecan dose adjusted based on UGT genotyping	No PK data	30%	30%
Sunitinib				
Carrato *et al*. (68); phase III	Sunitinib (37.5 mg 4 weeks on, 2 weeks off) + FOLFIRI	Stopped due to futility		
Tsuji *et al*. (69); phase II	Sunitinib (37.5 mg 4 weeks on, 2 weeks off) + FOLFIRI	Stopped early	96%	
Reardon *et al*. (70); phase I	MTD was 50 mg of sunitinib combined with 75 mg/m^2 of irinotecan	Moderate toxicity	32%	4%
Starling *et al*. (71); phase I	Sunitinib + FOLFIRI	MTD—sunitinib (37.5 mg 4 weeks on, 2 weeks off) + FOLFIRI	83.3%; 47.6% at MTD	33.3%; 14.3% at MTD
Boven *et al*. (72); phase I: solid tumours	MTD: sunitinib 25 mg per day (days 1–14) with irinotecan 250 mg/m^2 (day 1)	But no activity; 12% AUC ↑—irinotecan; 20% AUC ↑—SN-38	73%	100%—all grades
Qvortrup *et al*. (73); phase I	Sunitinib continuous-dosing with cetuximab and irinotecan every other week	25 mg daily—sunitinib	18% leukopenia	7%
Vandetanib				
Meyerhardt *et al*. (74); phase I	Vandetanib with cetuximab/ irinotecan 150 mg/m^2 weekly	MTD for vandetanib 200 mg	QT prolongation; 11% > grade 2 neutropenia	Diarrhoea grade 3 or 4: 29.6%
Saunders *et al*. (75); phase I	Vandetanib + FOLFIRI in CRC	Vandetanib—100/300 mg; AUC of: SN-38—↑25%; irinotecan—↑14%	19%	95%—all grades

FOLFIRI, folinic acid, infusional 5-fluorouracil, irinotecan; IFL, irinotecan, leucovorin and 5-fluorouracil; MTD, maximum tolerated dose; RP2D, recommended phase II dose; bid, twice daily; PK, Pharmacokinetics; N/R, not reported.

highlight the difficulties in optimizing the dosing schedule and reducing the overlapping toxicities due to pharmacokinetic and pharmacodynamics interactions. The efficacy/safety profile of the combination demonstrated *in vitro* and *in vivo* studies have not translated into clinical practice.

Individually, irinotecan and KIs are effective anticancer agents. However, as indicated earlier, when combined together the regimen is poorly tolerated with increased neutropenia and diarrhoea. Significant changes in pharmacokinetic profiles of irinotecan, its metabolite SN-38 as well as the KI, were commonly seen in phase I trials leading to lower MTDs. Moreover, frequent dose reductions and interruptions make the combination ineffective and impractical.

There are more than a hundred kinase inhibitors in different phases of development for the treatment of various cancers. Combination of KIs with chemotherapy or immunological agents may be useful to prevent drug resistance. To reduce the failure rate in future clinical trials, the rational design of combination regimens that includes KIs and cytotoxic drugs supported by strong preclinical information will be required. Although the success demonstrated in pre-clinical *in vitro* studies and animal models are often not reproduced in human clinical trials, these studies provide useful *in vivo* information that are of great relevance to predict possible risks and benefits during clinical trial conduct (80,81).

Based on the potential for strong pharmacokinetic interactions, a complete evaluation of metabolic pathways including interactions with CYP and UGT enzymes and transporters resulting transport-metabolism interplay is warranted before the new KIs could be combined with existing cytotoxic chemotherapeutic drugs especially irinotecan. Prior to embarking on expensive, large sample size Phase III trials with highly toxic combination therapies with potentially life threatening toxicities, well conducted good quality animal studies with the combination of a KI and irinotecan will be essential.

Moreover, there is an argument to include participants with various pharmacokinetic variants of UGT1A1 in the study population in early phase trials involving irinotecan with KI combination. A recently published single arm study with irinotecan dose escalated based on UGT1A1 genotyping along with a lower dose of regorafenib at 120 mg per day in a series of 13 patients demonstrated clinical efficacy with manageable toxicities (67). In this trial, the combination of irinotecan and regorafenib resulted in lower rates of severe neutropenia (30%) and diarrhoea (30%).

Conclusions

Combining a KI and irinotecan to treat various cancers has been challenging due to increased toxicity. While the admittedly limited preclinical studies show impressive anticancer activities, replicating the results in human trials has been hampered by the dose modifications required both for the kinase inhibitors and irinotecan due to the pharmacokinetic and pharmacodynamics interactions. Future trials would need to incorporate dose escalation strategies based on genotyping of metabolising enzymes and transporters in the early phase clinical trials to define optimal doses for further development of the combination.

Footnote

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