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Current Perspective

The use of oral cytotoxic and cytostatic drugs in cancer treatment

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Abstract

Although with a few exceptions, most new anticancer agents are initially developed for intravenous use, oral treatment with anticancer agents is, if feasible, to be preferred, as this route of administration is convenient to patients, reduces administration costs and facilitates the use of more chronic treatment regimens. Recent studies have identified various physiological barriers limiting the oral absorption of anticancer drugs. Presently, several strategies are explored to alter the low and variable oral bioavailability of several important anticancer agents by taking advantage of an intentional interaction between anticancer agents and drugs that modulate active intestinal drug transporters or (intestinal) enzymes.

Keywords: Oral drugs; Topotecan; Pharmacokinetics; Toxicity

With only a few exceptions, most new anticancer agents are initially developed for intravenous (i.v.) use. The most important reasons for this are (i) the fact that usually less gastrointestinal toxicity occurs, (ii) there is immediate bioavailability and instantaneous pharmacodynamic effects, (iii) there is a misconception that uniformly inter- and intrapatient variation in exposure are larger with oral than with i.v. use, and (iv) there is a possibility to modify the dosing rate or even halt the infusion if indicated. However, i.v. administration is associated with a number of major drawbacks that limit its general applicability, including (i) morbidity of gaining i.v. access, (ii) risk of catheter-related infections, (iii) potential thrombosis and extravasation, and (iv) the presence of particulate matter in the infusional preparations. In addition, in the search for more cost-effective treatment regimens, pharmacoeconomic considerations are increasingly important in choosing drug administration routes [1]. Further impetus for the development of extravascularly administered anticancer drugs has also been patient preferences and quality-of-life issues, which are becoming central considerations in palliative treatment regimens. Indeed, recent work from Liu and colleagues has indicated that approximately 90% of cancer patients expressed a preference for oral versus i.v. chemotherapy, predominantly because of the convenience of administration outside a clinical setting or current concerns or previous problems with i.v. access [2].

For the reasons mentioned, if equivalent safety and efficacy can be demonstrated, an all oral regimen in the palliative setting would be clearly a very welcome addition to the chemotherapeutic armamentarium. Indeed, the need to move cancer treatment from a predominantly hospital-based, inpatient setting into the ambulatory setting has in recent years led to a further exploration of anticancer agents that have been available for many years (e.g. etoposide, cyclophosphamide and idarubicin), and novel (synthetic) derivatives of fluoropyrimidines (e.g. UFT, capecitabine, S-1), platinum-coordinated agents (e.g. JM-216), and Vinca alkaloids (e.g. vinorelbine) [3]. In addition, the recognition that several compounds may require prolonged exposure to maximise pharmacodynamic effects through the use of chronic treatment has led to development of oral regimens for cell cycle specific agents such as the camptothecins (e.g. topotecan, 9-aminocamptothecin, irinotecan). Furthermore, the recent clinical investigations with agents acting on signal-transduction pathways involving farnesyl transferases (e.g. SCH66366 and R115777) or matrix metalloproteinases (e.g. SU6668, CGS27023A) has spurred great interest in oral drug administration in chemotherapeutic treatment of cancer patients [4].

The report by Gore and colleagues [5] in this issue of *European Journal of Cancer* highlights this issue elegantly for the topoisomerase I inhibitor, topotecan. These investigators designed a study to compare the

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efficacy, safety and tolerability of oral topotecan compared with the standard i.v. regimen in a similar group of patients (266 in total) with relapsed ovarian cancer. They were able to demonstrate that the toxicity in both groups was mainly haematological (principally neutropenia) with grade 4 toxicity occurring in a much higher proportion of i.v. courses (51%) than oral courses (15%), whereas a small, but significant, difference was also observed in the median overall survival in favour of the i.v. treatment (51 weeks versus 58 weeks; $P=0.033$). These findings are similar to those published recently with a comparative study of i.v. versus oral topotecan in patients with relapsed small-cell lung cancer [6].

In an effort to understand the relative reduction in the toxicity profile associated with oral topotecan compared with the i.v. treatment, a number of issues may be particularly relevant. It has been previously demonstrated that the absolute oral bioavailability of topotecan gelatin capsules in patients with solid tumours is $42\pm13\%$ (90% confidence limits, 37–47%) [7]. In the study designed by Gore and colleagues [5], patients were randomised to receive either oral topotecan at 2.3 mg/m^2/day or i.v. topotecan at 1.5 mg/m^2/day for 5 consecutive days, with treatment cycles repeated every 21 days (i.e. the dose recommended for further use after completion of phase I studies). When corrected for a hypothetical mean fractional bioavailability, the oral dose in each patient is ($2.3\times0.42=$) 0.97 mg/m^2/day, which is 35.5% lower than the dose administered to patients receiving i.v. topotecan. It can thus be anticipated, based on the linear dose-exposure relationships for topotecan, that the predicted cumulative area under the plasma concentration versus time curve (AUC) is similarly reduced with oral treatment. From previous studies, it is known that the topotecan AUC is significantly correlated with the percentage decrease in absolute neutrophil count [8], as well as with the antitumour activity [9]. Clearly, these latter attributes create added incentives for the differential haematological toxicity and overall survival in the current study. Thus it may be that the phase I studies underestimated the feasible oral dose and that a slightly higher oral dose would have yielded a more favourable outcome for the oral use, balancing side-effects with desired antitumour effects. It is speculated by Gore and colleagues that differences in peak plasma concentration between oral and i.v. topotecan may also play a role in the reduced neutrophil toxicity [5], although data from modelling kinetic–dynamic relationships have not revealed such relationships for topotecan [10]. Obviously, these issues could only be resolved through further randomised studies, in which adequate attention is given to the topotecan disposition characteristics, and/or by using pharmacokinetic–pharmacodynamic guided comparative trials. In any event, the studies reported suggest that oral and i.v. topotecan can be considered interchangeable [5,6].

1. Current developments — pharmacological considerations

The majority of drugs administered orally are intended to act systemically, and for these, absorption is a prerequisite for activity. Delays or losses of the drug during absorption may contribute to variability in the drug response, and occasionally, may result in the failure of the drug therapy. There are many anatomical and physiological factors affecting the overall rate and extent of drug absorption from the gastrointestinal tract, making a precise quantitative prediction difficult. Included among them are the physicochemical properties of the molecule, perfusion and pH, gastric emptying, reactions competing with absorption (e.g. acid hydrolysis), and factors controlling dissolution (e.g. surface area, solubility and precipitation). As discussed by DeMario and Ratain in Ref. [11], an ideal chemotherapeutic drug would have little interpatient variability in absorption and AUC and, more importantly, little intrapatient variability with successive doses. Since an inverse relationship has been found between decreasing absolute bioavailability of drugs and the interindividual variation in bioavailability, it is obvious that caution must be taken in prescribing oral drugs with low oral bioavailability as either toxic or sub-therapeutic dosing may easily occur [12].

Recently, various biochemical barriers have been implicated in the restriction of drug absorption that may be highly relevant for oral treatment with chemotherapeutic agents, particularly those having a low bioavailability. In particular, intestinal drug transporters and drug-metabolising enzymes have been shown to limit the intestinal absorption of some clinically important drugs [13]. Lack of or inadequate information about the involvement of these mechanisms during the early process of anticancer drug development invariably results in either unpredictable excessive side-effects or sub-optimal exposure in the clinical evaluation.

1.1. Intentional biomodulation

1.1.1. Intestinal drug transporters

One of the principal mechanisms that can explain the variable pharmacokinetics of anticancer agents given orally is the affinity for drug transporters expressed in the intestinal epithelium and directed towards the gut lumen. Thus far, three major classes of drug pumps, referred to as P-glycoprotein, multidrug resistance-associated protein (MRP1) and its homologue MRP2 (also referred to as cMOAT), and breast cancer-resistance protein (BCRP; also known as MXR or ABCP1), have been characterised, and may play a role in mediating transmembrane transport of anticancer drugs [14]. These proteins belong to the large superfamily of adenosine triphosphate (ATP)-binding cassette transporters that are found in almost all prokaryotic and

eukaryotic cells. The characteristic tissue distribution of the currently known drug transporters is highly indicative for a role in detoxification and protection against xenobiotic substances. Indeed, genetic knockout of murine P-glycoprotein genes has shown increased intestinal absorption of a variety of substrate drugs commonly used in clinical oncology, including paclitaxel and topotecan [15,16]. The results obtained in these so-called knockout mice have been the starting point for various proof of concept studies in cancer patients, by administering taxanes (i.e. paclitaxel and docetaxel) in combination with cyclosporin A (a P-glycoprotein inhibitor) or topotecan in combination with GF120918 (a potent inhibitor of P-glycoprotein and BCRP) [17]. These clinical investigations have shown the possibility of modulating the oral bioavailability of anticancer agents by the use of specific inhibitors of active drug transporters.

Clearly, modulation of the intestinal absorption of anticancer drugs that are substrates of active pumps is further complicated by the recent recognition that polymorphic transporters exist that can modulate drug uptake. For example, it was shown recently that polymorphism of P-glycoprotein is significantly correlated with reduced protein expression levels in the duodenum and with increased plasma concentrations of a substrate drug, digoxin [18]. This indicates that P-glycoprotein polymorphism is expected to affect the absorption and tumour concentrations of numerous other substrates of P-glycoprotein, such as the taxanes and topotecan, and suggests that dosage modifications based on pharmacogenetic analysis may be of great importance for the future treatment of cancer patients.

1.1.2. Intestinal enzymes

As previously mentioned, high extraction of anticancer drugs by extensive metabolism in the gut wall and/or the liver during first-pass (i.e. prior to reaching the systemic circulation) is another mechanism involved in the variable oral availability of various agents. Indeed, the activity of metabolic enzymes, particularly the cytochrome P450 (CYP) isozyme 3A4 explains the low and variable bioavailability of numerous drugs [11]. Furthermore, extensive and variable biotransformation by CYP3A4 can result in formation of one or more polar metabolites with pharmacological activity, which may be equal or even higher than that of the parent drug. The combined intentional use of a CYP3A4 substrate anticancer drug (e.g. etoposide) given with specific inhibitors of enzyme activity (e.g. ketoconazole) for the purpose of decreasing interindividual variability in drug effects and to maximise drug absorption, has recently been considered [19].

In addition to CYP3A4, a number of other enzymes expressed in intestinal cells may play a major role in oral anticancer drug pharmacokinetics. For example, it has been suggested that formation of the pharmacologically active metabolite of irinotecan (viz. SN-38) is increased with oral administration compared with i.v. dosing, as a result of presystemic conversion of irinotecan by an intestinal carboxylesterase enzyme, which is known to be expressed at high levels in human intestinal tissues [20]. Similarly, implementation of combined use of inhibitors of dihydropyrimidine dehydrogenase (DPD), the initial and rate-limiting enzyme involved in degradation of various pyrimidines, is now being considered view. For example, eniluracil (a specific inactivator of DPD) administered to cancer patients before oral dosing of the anticancer agent 5-fluorouracil increased the bioavailability to approximately 100% [21].

1.2. Unintentional drug–drug interactions

Obviously, there is considerable motivation for understanding adverse drug interactions with (anticancer) agents, particularly when administered orally, because of their narrow therapeutic index, and the numerous concomitant medications that are administered routinely or intermittently. Indeed, drug interactions with various agents, including anticancer drugs, are a major cause of morbidity and mortality in modern clinical practice, causing over 100 000 deaths per year in the United States alone [22]. Substantial progress has been made recently towards a proper understanding of drug interactions resulting in increased chemotherapy-induced toxicity. In contrast, much less is known about concomitant medications resulting in metabolic inactivation of anticancer drugs given orally as a result of the induction of drug transporters or enzymes. Recent studies have shown, for example, that induction of intestinal P-glycoprotein and MRP2 by rifampin appears to be the underlying mechanism of decreased plasma concentrations of substrates, including digoxin and drug conjugates (such as the beta-glucuronide conjugate of the irinotecan metabolite, SN-38), with concomitant rifampin therapy [23]. This suggests an underrated new type of steady-state drug interaction affecting compounds, likely including several anticancer drugs, that are subject to transport rather than metabolism. Similarly, induction of several enzymes, including CYP3A4, by some medications has been described and may have a serious impact on anticancer therapy. For example, use of St. John's Wort extracts has been shown to result in an increased expression of CYP3A4 and significantly increased clearance or decreased bioavailability of frequently prescribed drugs (like theophilline, cyclosporin A and indinavir), leading to complete loss of therapeutic effects [24]. In view of the major role of this enzyme in anticancer drug disposition, it is expected that induction of CYP3A4 expression by St. Johns Wort extracts will result in altered drug clearance and affect toxicity profiles and possibly antitumour

activity. With these kind of potential implementations for the oral administration of anticancer agents, particularly in an outpatient setting, these intriguing results clearly deserve further investigation in the field of anticancer drug pharmacology.

2. Patient compliance to oral drugs

A frequently expressed concern of physicians is the compliance of patients in taking their oral medication. It is unclear why this concern is raised in relation to cytotoxic agents and never expressed when hormonal treatment of cancer is discussed. Hormonal treatment of cancer is routine practice and invariably involves oral agents, and results obtained with these agents suggest that patient compliance is not really an issue. In our view, this is also the case for oral cytotoxics. Recently published large randomised trials [5,6,25–28] involving close to 2000 patients have shown that (i) toxicity is usually less with oral agents, and (ii) outcome is comparable, or even superior for the oral agent compared with the i.v. treatment [27,28]. If overall outcome is not affected by use of the oral agent, it is safe to conclude that (in general) patient compliance, at least for the use of oral cytotoxics to treat cancer, is not really an issue.

3. Conclusions and future directions

Oral treatment with anticancer agents is, if feasible, to be preferred, as this route of administration is convenient to patients, reduces administration costs and facilitates the use of more chronic treatment regimens. Recent studies have identified various physiological barriers limiting the oral absorption of various anticancer drugs, and several strategies are now underway using pharmacological modulation to alter the low and variable oral bioavailability of several important anticancer agents, including the taxanes (paclitaxel and docetaxel), epipodophyllotoxins (etoposide and analogues), and camptothecin derivatives (e.g. topotecan). However, before taking advantage of intentional interactions between anticancer drugs and agents specifically administered to modulate active intestinal drug transporters or (intestinal) enzymes, a number of important questions need to be answered. Most importantly, it will be essential to demonstrate the clinical feasibility of these approaches and show in comparative studies similarity in the antitumour activity efficacy with standard i.v. dosing regimens. Regardless of the potential physiological barriers mentioned, the outcomes of large randomised trials, such as the one conducted by Gore and colleagues [5], indicate that i.v. and oral cytotoxic agents are easily interchangeable, and that the concerns raised about patient compliance seem to be unjustified. Given this observation and the work currently ongoing to further limit inter- and intrapatient variation in systemic exposures, it is clear that oral drugs for cancer treatment have a future and will likely play a more important role than they did in the past.

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