Risk Management and Healthcare Policy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

The Rate of Infusion Represents an Important Aspect of Administering Anticancer Agents

Mei-Juan Lan[1], Di-Fei Yao[2,3], Ling-Ling Zhu[4], Quan Zhou[2]

[1]Division of Nursing, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang Province, People's Republic of China; [2]Department of Pharmacy, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang Province, People's Republic of China; [3]Key Laboratory of Intelligent Pharmacy and Individualized Therapy of Huzhou, Changxing Campus of the Second Affiliated Hospital of Zhejiang University, Huzhou, Zhejiang Province, People's Republic of China; [4]VIP Geriatric Ward, Division of Nursing, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang Province, People's Republic of China

Correspondence: Quan Zhou, Department of Pharmacy, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Jiefang Road No. 88, Shangcheng District, Hangzhou, Zhejiang Province, 310009, People's Republic of China, Email zhouquan142602@zju.edu.cn; Ling-Ling Zhu, VIP Geriatric Ward, Division of Nursing, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang Province, People's Republic of China, Email 2192022@zju.edu.cn

Background: Infusion rate is one of the essential elements that should be included in all intravenous orders. Patients may experience adverse consequences or risks associated with inappropriate infusion. Meanwhile, there is growing pressure on the chemotherapy unit to deliver treatment quickly, efficiently, and safely, and thus it is very necessary to improve the chemotherapy process and service to cancer patients. Clinicians should consider how to further standardize infusion therapy, and innovate new infusion strategies to increase efficacy, reduce toxicity, improve patient satisfaction and save health resource costs. Sporadic studies have evaluated the effects of infusion rates of anticancer agents on clinical outcomes, economic benefits, and administration efficiency. However, an update review has not been available.

Methods: Relevant literature was identified by search of PubMed until September 2023.

Results: Infusion rates may have significant effect on the efficacy of anticancer agents (e.g., methotrexate, fluorouracil, and arsenic trioxide). Slow infusion is safer for platinum compounds, doxorubicin and carmustine, whereas fast infusion is safer than slow infusion of gemcitabine. Optimal flow rates of paclitaxel and fluorouracil are based on the balance between multiple risks of toxicity. Optimal infusion rate may bring economic benefits. If efficacy and safety are not compromised, shortened infusion may result in higher patient satisfaction, improved institutional efficiency and more nursing time available for other activities (e.g., biosimilar products, endostar). Other concerns about infusion rate include clinical indications (eg, paclitaxel and rituximab, methotrexate), severity and type of hypersensitivity reactions (e.g., platinum compounds), formulation features (e.g., paclitaxel, doxorubicin), and genetic polymorphism (e.g., gemcitabine, methotrexate).

Conclusion: The latest knowledge of infusion rate concerns will enhance the appropriateness and accuracy in intravenous administration. Interdisciplinary teams should collaborate and implement relevant risk management and healthcare policy. It is worthwhile to conduct comparative studies of intravenous therapy with different infusion speeds.

Keywords: anticancer agents, efficacy, healthcare policy, infusion rate, medication administration, pharmacoeconomics, safety

Introduction

Infusion rate is one of the essential elements that should be included in all intravenous orders according to *Joint Commission International Accreditation Standards for Hospitals* (7th Edition).[1] Also, American Society of Hospital Pharmacists (ASHP) guidelines define best practices for the safe use of chemotherapy and biotherapy agents and emphasized that the administration rate should be specified in standardized medication-order forms when relevant.[2]

Meanwhile, it is important to make sure that the fluid will be infused at the prescribed rate. However, prescribed infusion rate may not be closely adhered to by nurses. An observational study showed that incorrect duration of infusion accounted for 26% of medication administration errors in chemotherapy infusion for pediatric inpatients in India.[3] We reported an infusion rate-related chemotherapy incident in 2010, i.e., a gastric cancer patient unfortunately received less

Received: 30 September 2023
Accepted: 18 November 2023
Published: 22 November 2023

than 30 minutes infusion of fluorouracil (5-FU) 3.5 g that should be administered over 40 hours at a speed of 4 mL/hour.[4] Park et al explored nurses' experiences with infusion nursing practice, and found that nurses experienced high levels of stress when administering infusions in the correct dose and rate for patient safety.[5] Therefore, much attention should be paid to the awareness of specifying appropriate infusion rate and the accuracy of intravenous administration.

Also, there is growing pressure on the chemotherapy unit to deliver optimal treatment, and thus it is very necessary to improve the chemotherapy process and service to cancer patients.[6] Clinicians should consider how to further standardize intravenous infusion therapy, and innovate new infusion strategies to increase efficacy, reduce toxicity, improve patient satisfaction and save health resource costs. Sporadic clinical studies have been conducted to evaluate the effects of infusion rates on therapeutic and economic outcomes of anticancer agents. New findings are instructive for clinicians although they may challenge the regular infusion regimen according to the package inserts. An update review is unavailable in this respect. Therefore, we wrote this narrative review in order to bring the latest advances to the clinicians and to promote research and practical exploration in this area.

Methods

Search Strategy

Potentially relevant literature until September 2023 was identified by performing searches in PubMed. The search methods were as follows: (1) Searching each paper with title containing a phrase (i.e., infusion rate, rate of infusion, short infusion, fast infusion, rapid infusion, accelerated infusion, slow infusion, extended infusion, prolonged infusion, infusion duration, infusion method, infusion time, administration styles, different schedules, delivery methods); (2) Searching each paper with all fields containing cancer, tumor, neoplasm, or carcinoma.

Selection Criteria

Two reviewers (LMJ and YDF) independently retrieved the literature and screened the relevant studies. If they had a disagreement over including or excluding an article, the third reviewer (QZ) was consulted. Three hundred and fifty-four articles were identified. Documents such as books and documents, comments, letters, reviews, meta-analyses, systematic review, case reports, or editorials were excluded despite being retrieved using the search terms (n=46). After reviewing the abstracts, documents were excluded due to lack of comparing outcomes of different infusion rates (n=271). Full-text articles were further assessed for eligibility. Animal studies and descriptive studies without statistical analysis, or without control group were also not included in this review (n=6). Thirty-one papers were finally chosen according to the inclusion/exclusion criteria (Figure 1). Valuable information was summarized by data interpretation.

Results

Influence of Infusion Rate on the Efficacy of Anticancer Agents

Methotrexate

Hiraga et al investigated the correlation of infusion schedules with methotrexate (MTX) penetration into cerebrospinal fluid, tumor response, and survival. 100 mg/kg MTX was administered on either a rapid (3-hour) or regular (6-hour) infusion schedule for two or three cycles. Rapid infusion significantly increased levels of MTX in the cerebrospinal fluid and resulted in significant tumor volume reduction in primary central nervous system lymphomas ($P< 0.001$).[7]

5-FU

Compared with bolus administration in advanced colorectal cancer patients, continuous infusion of 5-FU had a significantly high tumor response rate and overall survival (overall hazards ratio 0.88; P=0.04).[8] In most of the studies, the cumulative dose of 5-FU following continuous infusion was two to three times higher than with bolus infusion. Such higher dose and the prolonged exposure of tumor cells to the drug may explain the better results of continuous infusion over bolus infusion. However, Hoshino et al investigated the effects of two different schedules of 5-FU at relatively low dose (200 mg/day) on each day for 5 days preoperatively on DNA and RNA damage in tumor tissue specimens from colorectal cancer patients. It was observed that rapid infusion over 3–4 minutes was more effective than continuous infusion in RNA damage in tumor tissue while the thymidylate synthetase inhibition rate was higher in rapid infusion

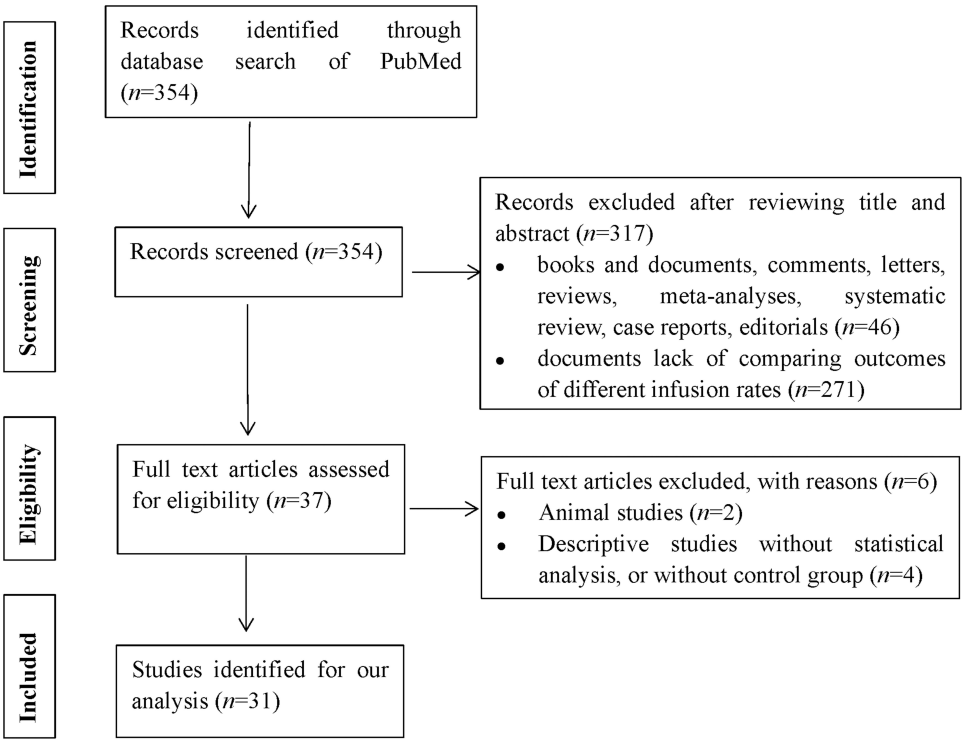

Figure 1 Flow chart showing selection of literature.

group compared with continuous group in cases involving lymph node metastasis.[9] Therefore, it continues to be necessary to examine the relationship between 5-FU efficacy and different methods of administration.

Arsenic Trioxide

Zhou et al studied the effects of administration styles of arsenic trioxide (0.16 mg/kg daily) on leukocytosis. Compared with the routine regimen (45–55 drips per minute with total infusion duration 2–3 hours daily), the continuously slow infusion regimen (8 drips per minute with total infusion duration 18–21 hours daily) can obtain high efficiency of apoptosis and low differentiation proportion, relieve leukocytosis, and gain maximal therapeutic benefit.[10]

Influence of Infusion Rate on Safety of Anticancer Agents

Slow Infusion is Safer Than Fast Infusion

Carboplatin

Compared with standard-infusion (over 30 or 60 minutes) carboplatin, 3-h extended-infusion carboplatin resulted in a lower incidence of hypersensitivity reactions (HSRs) in patients with ovarian, fallopian tube, or peritoneal cancer (40% versus 24.2%, P=0.00275).[11] O'Cearbhaill et al observed that an incrementally increasing, prolonged 3-hour infusion of carboplatin with appropriate premedication could reduce the occurrence rate of HSRs compared with the standard 30-minute schedule in sequentially treated patients (3.4% versus 21%, P<0.001), indicating that prophylactic conversion to a prolonged infusion during carboplatin retreatment may be of clinical relevance.[12] However, a decreased HSR rate was not observed in women with recurrent ovarian cancer following a prophylactic, 3-hour extended carboplatin infusion; LaVigne et al suggested that this may be because the study was underpowered to show a difference between the arms.[13]

Oxaliplatin

A randomized study revealed that prolonged infusion (6 hours) over the conventional schedule (2 hours) could significantly reduce acute and possibly chronic oxaliplatin-induced neurotoxicity in colon and gastric cancer patients receiving oxaliplatin-based regimen as adjuvant chemotherapy. Prolonged infusion group experienced statistically lower

percentage of patients with grade ≥2 neurotoxicity compared with conventional infusion group (28.1% versus 59.3%; P=0.02).[14] A retrospective, cohort study evaluated the safety outcomes of rapid infusion of oxaliplatin compared with standard infusion in patients receiving oxaliplatin-based chemotherapy regimen. Compared with standard infusion group, rapid infusion group needed minimal treatment modifications (e.g., dose reduction, delayed dose, or slowed infusion rate), but it was associated with increased rate of permanent oxaliplatin discontinuation (7.8% versus 1.1%, P=0.032) and peripheral neuropathy (72.2% versus 42%, P< 0.001).[15]

Cisplatin

A randomized controlled trial studied the infusion strategy of cisplatin 50 mg/m^2 in treatment of squamous cell carcinoma of the uterine cervix. Continuous infusion over 24 hours produced significantly less nausea and vomiting than rapid infusion (1 mg/min) under the premise of standardized antiemetic therapy for both regimens. With respect to the response rate and frequency of other adverse reactions, no statistically significant differences were presented between the two groups.[16] An observational, retrospective study revealed that the incidence of nephrotoxicity in patients with lung carcinoma was not affected by the infusion rate of cisplatin (1-hour rapid infusion versus 3-hour regular infusion). Therefore, a 1-hour rapid infusion of cisplatin is a safe and feasible method, which may potentially shorten hospital stay and enable treating patients in the outpatient setting.[17]

Doxorubicin

A prospective randomized controlled trial confirmed that prolonged infusion of doxorubicin (6 hours) could reduce cardiotoxicity compared with standard infusion (15–20 minutes) in 62 consecutive patients with metastatic carcinoma of the breast or carcinoma of the ovary Stage III or IV.[18] However, data from two recent studies among patients with sarcoma treated with doxorubicin suggested that prolonged continuous intravenous infusion was not associated with superior outcomes over bolus infusion within doxorubicin dosing limits and it has not been effective as a strategy to mitigate cardiac events.[19,20]

Carmustine

Infusion reactions are common after high-dose carmustine in BEAM chemotherapy (carmustine, etoposide, cytarabine, and melphalan) and are not reduced by lengthening the time of administration (90 minutes versus 120 minutes).[21] Reconstituted solution of carmustine (0.2 mg/mL) should be administered by slow intravenous infusion over at least 2 hours and the infusion rate should not be more than 1.66 mg/m²/min, otherwise it can lead to pain and burning at the site of injection.[22]

Fast Infusion is Safer Than Slow Infusion

Gemcitabine

Gemcitabine administration is a typical case. The package insert of gemcitabine recommends that each intravenous infusion is over 30 minutes and prolongation of the infusion time beyond 60 minutes would increase incidence of hypotension, severe flu-like symptoms, myelosuppression, and asthenia. The half-life and volume of distribution of gemcitabine could be significantly influenced by infusion rate.[23] Compared with infusion rate >25 mg·m^{-2}·min^{-1}, infusion rate below this value resulted in two-fold higher formation clearance and exposure of active triphosphate metabolite (dFdCTP) in patients with solid tumors receiving gemcitabine.[24] A randomized Phase II trial in advanced non-small cell lung cancer (NSCLC) patients showed that prolonged gemcitabine infusion at 10 mg·m^{-2}·min^{-1} for 150 minutes resulted in higher occurrence of grade 3–4 neutropenia compared with standard infusion (30 minutes) of the equivalent dose (49.2% versus 17.9%, P=0.0002).[25]

Optimal Flow Rate Based on Balanced Considerations

5-FU

The 5-FU-associated cardiotoxicity was largely schedule-dependent. Continuous intravenous administration of 5-FU for 5 consecutive days has a higher cardiotoxicity than bolus administration (12.5% versus 2.4%, P<0.019).[26] Grade 3 or 4 hematologic toxicity was more frequent in patients receiving bolus infusion compared with continuous infusion of 5-FU

(31% versus 4%; $P<0.0001$), whereas hand-foot syndrome was more frequent in the continuous infusion group (34% versus 13%; $P<0.0001$).[27] Therefore, bolus infusion in combination with continuous infusion is usually used, e.g., recommended dose of 5-FU for colon, rectum, and pancreatic adenocarcinoma, is 400 mg/m^2 intravenous bolus on Day 1, followed by 2400 mg/m^2 intravenously as a continuous infusion over 46 hours every 2 weeks, in combination with leucovorin or as a component of a multidrug chemotherapy regimen that includes leucovorin.

Paclitaxel

The plasma clearance of solubilizing agent Cremophor EL (CrEL) increased significantly when the infusion duration of CrEL-based paclitaxel was prolonged from 1–3 to 24 hours ($P<0.05$) whereas the area under the curve (*AUC*) of CrEL increased disproportionally with shortening of infusion.[28] It indicates that prolonged infusion may be of clinical relevance due to the association of CrEL with the frequent occurrence of acute HSRs in paclitaxel infusion therapy. Jennens et al observed that the 24-hour infusion regimen caused significantly worse neutropenia than the 3- or 6-hour infusion regimens whereas prolonging the duration of paclitaxel infusion from 3 to 6 hours did not significantly increase the degree of neutropenia.[29] Gelderblom et al compared the pharmacokinetics of unbound paclitaxel during 1- and 3-hour infusions of paclitaxel 100 mg/m^2. The 1-hour infusion schedule had substantially lower *AUC* of unbound paclitaxel and significantly higher *AUC* of CrEL than the 3-hour schedule ($P<0.05$). Taken together, short-infusion schedules would reduce myelotoxicity while increasing potentially CrEL-related side effects.[30] The 3-hour infusion schedule of CrEL-based paclitaxel is optimal based on balanced considerations.

Influence of Infusion Rate on Economic Efficiency of Anticancer Agents

If efficacy and safety are not compromised, shortened infusion may result in higher patient satisfaction, improved institutional efficiency and more nursing time available for other activities. For biosimilar monoclonal antibodies, fast infusion seems more economic than slow infusion.

Bevacizumab

According to the prescribing information for bevacizumab, infusion time is 90 min in the first dose, 60 minutes in the second, and then from the third dose it is 30 min if no HSR occurs in the first two doses. A short bevacizumab infusion regime comprising an initial infusion for 30 minutes followed by a second infusion at 0.5 mg/kg/min is safe and efficacious for the management of colorectal cancer.[31] The feasibility of rapid bevacizumab infusion in 30 minutes at the first time has been confirmed, thereby resulting in a significant reduction in chemotherapy chair time and nursing workload.[32,33]

Rituximab

According to rituximab dosage guide, standard infusion after the first intravenous administration is to initiate infusion at a rate of 100 mg/h and increase rate by 100 mg/h increments at 30-minute intervals to a maximum of 400 mg/h in the absence of infusion toxicity.[34] A prospective study in patients receiving at least one rituximab infusion showed that rapid 90-minute infusion rather than standard infusion could reduce infusion time by 110.5 minutes per infusion and clinic visit time by 92 minutes per outpatient encounter if prophylactic acetaminophen and diphenhydramine were administered prior to each infusion.[35] Moore et al developed a pharmacist-driven protocol allowing pharmacists to change the administration schedule to rapid infusion. The implementation of this protocol led to a significant improvement in the use of rapid infusion rituximab and optimized chair time utilization, while no infusion-related reaction (IRR) was observed.[36]

Daratumumab

Daratumumab is an anti-CD38 monoclonal antibody initially approved as a single agent for the treatment of relapsed and refractory multiple myeloma. Stakiw et al confirmed the safety profile and anti-myeloma effects of accelerated daratumumab infusions commencing with the second dose (i.e., all subsequent doses were given over 90 minutes after an initial dose on Cycle 1 Day consisting of 8 mg/kg over 4 hours). The rapid infusion protocol has resulted in more efficient resource utilization and has become the standard protocol for use in all intravenous daratumumab regimens in

Canada.[37] Issam et al confirmed the safety, tolerability, and economics of rapid daratumumab infusion for patients with relapsed/refractory disease. A 52-week regimen of daratumumab infused at rapid rates can save up to $15,000 over the regular regimen infused at standard rates.[38]

Ramucirumab

For ramucirumab, shortening infusion duration from 60 to 30 minutes did not affect its clinical efficacy or overall safety profile (e.g., immediate IRRs) and may be clinically beneficial for patients and healthcare providers.[39] Prescribing information for ramucirumab has been updated for all approved cancer indications, allowing the approach that administers the initial infusion over the currently approved 60 minutes and, if no IRR is observed, reduce this duration to 30 minutes for subsequent infusions.[40]

Endostar

Endostar is a novel recombinant human endostatin that exerts its anti-angiogenic effects via vascular endothelial growth factor-related signaling pathways. It was approved by the State Food and Drug Administration of China in September 2005 as a treatment option for NSCLC. A retrospective study in our institution revealed that the continuous infusion of endostar (i.e., 15 mg of endostar was diluted in 250 mL of normal saline and infused daily at the rate of 11 mL per hour using an automatic infusion pump via a central line from day 0 to 8 prior to the chemotherapy) was not inferior to the intravenous drip administration (i.e., 15 mg endostar was diluted in 500 mL of normal saline and administered by intravenous drip over 4 hours from day 0 to day 13 before chemotherapy) in terms of response rate, disease control rate and adverse reaction profile in patients with locally advanced or metastatic lung squamous cell carcinoma concurrently receiving a gemcitabine/cisplatin regimen. Moreover, continuous infusion can reduce the total dose of endostar per cycle by 35.7% compared with traditional intravenous drip administration (i.e., 1 patient could save CNY 4307 per cycle on endostar according to the price of endostar in 2015), indicating that the continuous infusion may be a more economical choice.[41]

Discussion

Clinical Indication Concerns

For the same medicine, the optimal infusion time may be disease-specific. Therefore, pharmacists and nurses should be familiar with patient diagnosis during appropriateness review and intravenous drug administration.

For paclitaxel, package insert specifies such information. Two infusion regimens of paclitaxel (i.e., 3-hour infusion at a dose of 175 mg/m^2 or 24-hour infusion at a dose of 135 mg/m^2 every 3 weeks followed by cisplatin), are appropriate for previously untreated patients with ovarian cancer. However, the 24-hour infusion regimen is recommended for treatment of NSCLC whereas the 3-hour regimen is for treatment of metastatic breast cancer and adjuvant treatment of node-positive breast cancer.[42]

For previously untreated follicular non-Hodgkin's lymphoma (NHL) and diffuse large B-cell lymphoma (DLBL) patients, a 90-minute rapid infusion of rituximab can be administered in Cycle 2 with a glucocorticoid-containing chemotherapy regimen if patients did not experience a Grade 3 or 4 infusion-related reaction during Cycle 1. However, this rapid infusion regimen is not specified for other indications according to the package insert. Moreover, the 90-minute rapid infusion should not be administered to previously untreated follicular NHL and DLBCL patients who have clinically significant cardiovascular disease or who have a circulating lymphocyte count $\geq$ 5000/mm^3 before Cycle 2.[43]

MTX exhibits disease-specific requirements for infusion rates despite the prescribing information not describing such information. A randomized prospective clinical trial showed that the 24-hour infusion of high-dose MTX (1 g/m^2) could achieve significantly higher levels of MTX polyglutamates in bone marrow leukemia cells, and better anti-leukemic effects than the 4-hour infusion. The greatest effect of longer infusion was observed in hyperdiploid acute lymphoblastic leukemia (ALL). Greater anti-leukemic effects were still observed in T-cell ALL patients receiving 24-hour infusion rather than 4-hour infusion, despite the inter-group difference in MTX polyglutamates becoming smaller. However, infusion duration had no significant impact on MTX polyglutamates accumulation and anti-leukemic effects in ALL with the t(12;21)/(ETV6-RUNX1) chromosomal translocation.[44]

Concerns About the Severity and Type of HSRs

Hypersensitivity reaction is a common adverse reaction of platinum, with an incidence varying from 5% to 25%.[45] Desensitization protocols of platinum compounds are recommended for patients with HSRs. Prolongation of platinum infusion time is one measure of desensitization. Patients with moderate to severe platinum allergy were given platinum at different infusion rates depending on their risk with identical premedication. O'Malley et al described the method of triaging patients to appropriate desensitization protocols according to clinical categorizations based on severity and type, i.e., a shortened protocol was applied in patients with the lowest risk (i.e., the total infusion time was 1.5 hours for carboplatin in 500 mL, 2.25 hours for cisplatin in 1000 mL, and 3–4 hours for oxaliplatin in 500 mL), whereas stand or prolonged schedule could be used as the patient's risk increased (i.e., the infusion time could be extended to carboplatin 4.25 hours or 9 hours, cisplatin 5.25 hours or 14 hours, and oxaliplatin 5 hours or 9 hours).[46]

Formulation Feature Concerns

New formulations may overcome the defect of infusion regimen due to special requirements on infusion rate. Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) is a CrEL-free formulation for treatment of metastatic breast cancer, NSCLC, and adenocarcinoma of the pancreas. Unlike CrEL-based paclitaxel, nab-paclitaxel can be given at the dose of 260 mg/m^2 as a 30-minute intravenous infusion every 3 weeks with advantages (e.g., non-premedication required, shorter infusion time, higher maximum tolerated dose of paclitaxel and safer toxicity).[47]

A time and motion study in breast cancer patients in China showed the overall efficiency and cost-saving potential associated with nab-paclitaxel relative to paclitaxel. The mean total time for nab-paclitaxel and paclitaxel delivery (preparation, administration, premedication, total chair time, and adverse effects management) was 84 and 282 minutes, respectively (P<0.001), with the associated costs being US$59 and 254, respectively, per dose (P<0.001).[48]

In accordance with package insert of doxorubicin hydrochloride injection, it should be administered as an intravenous bolus (not less than 3–5 minutes). For doxorubicin liposome, the first dose should be administered at an initial rate of 1 mg/min after diluting the doses up to 90 mg in 250 mL of 5% dextrose injection. If no infusion-related adverse reactions are observed, increase the infusion rate to complete the administration of the drug over one hour.[49]

Genetic Polymorphism Concerns

Gemcitabine is used for the treatment of several solid tumours and exhibits high inter-individual pharmacokinetic variability. Khatri et al revealed that the presence of homozygous major allele for solute carrier family 28 member 3 (*SLC28A3*) (CC genotype) was associated with an almost two-fold increase in the formation clearance of dFdCTP metabolite whereas a synonymous SNP in the coding region of *SCL28A3* (*rs7867504; T>C*) was related to decreased dFdCTP formation clearance.[24] Saturation of nucleoside transporters (e.g., SLC29A1, SLC28A1, and SLC28A3) at higher infusion rate could result in the decrease in formation of intracellular dFdCTP. Metharom et al demonstrated that the pharmacological advantage of prolonged-infusion gemcitabine was restricted to patients with variant alleles of cytidine deaminase *c.79A>C*.[50] Therefore, there may be a greater advantage of administering gemcitabine at fixed dose rate (10 mg·m^{-2}·min^{-1}) to selected patients with genetic variation in key transporter/metabolic pathway proteins rather than an unselected population.

MTX is another example. Organic anion transporting polypeptide 1B1 (OATP1B1), a transmembrane hepatic uptake transporter encoded by the solute carrier organic anion transporter family member 1B1 (*SLCO1B1*) gene, is known to transport MTX. A multivariate general linear model revealed covariates related to MTX clearance. Compared with 4-hour infusion of a 2 g/m^2 dose, 24-hour infusion of a 1 g/m^2 dose was significantly associated with higher clearance. Meanwhile, with each copy of the *C* allele at *rs4149056*, the MTX clearance was reduced by 12 mL/min/m^2, and thus clearance is approximately 13% lower in patients with *CC* versus *TT* genotypes at *rs4149056*, which could have significance for efficacy or adverse events.[51] Patients with *CC* genotypes receiving 4-hour infusion regimen would be more likely to develop toxic symptoms due to lower MTX clearance. Therefore, pharmacogenetic consideration might be necessary when prescribing an infusion regimen of MTX. It is interesting to develop an individualized dosing strategy based on both genotype and infusion rate.

A summary of information for optimal infusion rate of anticancer agents is presented in Table 1.

Table 1 Concerns About Choice of Infusion Rate of Anticancer Agents

Multiple Concerns	Typical Medications	Rationales and Recommendations
Efficacy	Methotrexate	Rapid infusion could improve efficacy of methotrexate in primary central nervous system lymphomas.[5]
	Fluorouracil	Continuous infusion could achieve better efficacy compared with bolus administration in advanced colorectal cancer patients.[6]
	Arsenic trioxide	Slow infusion could obtain high efficiency on leukocytosis.[8]
Safety	Platinum compounds, doxorubicin, carmustine	Slow infusion is safer than fast infusion.[9–20]
	Gemcitabine	Fast infusion is safer than slow infusion.[22,23]
	Paclitaxel, fluorouracil	Optimal flow rates for paclitaxel and fluorouracil are based on the balance between multiple risks of toxicity.[24–28]
Economic efficiency	Biosimilar monoclonal antibodies (bevacizumab, rituximab, daratumumab, ramucirumab)	The optimal infusion rate may bring economic benefits (e.g., higher patient satisfaction, improved institutional efficiency and more nursing time available for other activities).[29–38]
	Endostar	Continuous infusion may be a more economical choice compared with traditional intravenous drip administration.[39]
Clinical indications	Paclitaxel, rituximab, methotrexate	These medications may exhibit disease-specific requirements for infusion rates.[40–42] Pharmacists and nurses should be familiar with patient diagnosis during appropriateness review and intravenous drug administration.
Severity and type of hypersensitivity reactions	Platinum compounds	It is wise to triage patients to appropriate desensitization protocols (e.g., shorten, stand, or prolonged) according to clinical categorizations based on severity and type of HSRs.[44]
Formulation features	Nanoparticle albumin-bound paclitaxel, doxorubicin liposome	New formulation can overcome the defect of infusion regimen due to special requirements on infusion rate.[45–47]
Genetic polymorphism	Gemcitabine, methotrexate	It is interesting to develop an individualized dosing strategy based on both infusion rate and genotype [gemcitabine: *SCL28A3* (*rs7867504*; T>C), *CDA c.79A>C*; methotrexate: *CC* genotypes at *SLCO1B1 rs4149056*][22,48,51]

Abbreviations: CDA, cytidine deaminase; SCL28A3, solute carrier family 28 member 3; HSRs, hypersensitivity reactions; SLCO1B1, solute carrier organic anion transporter family member 1B1.

New Horizon and Further Opportunities

There is a new horizon for clinicians to pay attention to infusion rate-related practice and research. The latest knowledge of infusion rate-related safety, efficacy, and pharmacoeconomics will enhance the awareness of appropriateness of infusion regimen and the accuracy in intravenous administration among clinicians. Regarding intravenous infusion therapy, healthcare policy should fully consider nursing workload, resources utilization, infusion center efficiency, cost, patient satisfaction, and patients' quality of life. The pharmacy and therapeutics committee should draft institutional protocol for optimal infusion rate of medications and implement extensive quality assurance monitoring (e.g., retrospective analysis of guideline compliance).

There are many further research opportunities in clinical practice, e.g., conducting head-to-head comparative studies of infusion regimens with different infusion rates from the perspectives of efficacy, safety, and cost-effectiveness, designing prospective comparative studies to control the study bias (e.g., the impact of each variable alone such as infusion time and premedications on the incidence of HSRs may not be differentiated), developing an individualized dosing strategy based on both genetic polymorphism and infusion regimen, and implementing effective interventions to enhance the accuracy of infusion rates. Evidence-based practice would provide support to revise infusion rate relevant prescribing information for some medications.

Conclusion

Infusion rate may have a significant impact on drug efficacy, safety, economic benefits, and administration efficiency. It should be specified in infusion orders of anticancer agents, and much attention should be paid to the accuracy of intravenous administration. It is very necessary to improve the chemotherapy process and service to cancer patients by delivering treatment quickly, efficiently, and safely. Interdisciplinary teams, consisting of nurses, pharmacists, physicians, information engineers, and hospital administrators, should collaborate to pay much attention to infusion rate-related practice and research. Risk management and healthcare policy should be drafted and implemented with the ultimate goal of improving patient quality of life.

Acknowledgments

This work was supported by Program of Hospital Pharmacovigilance Research Association (No. DRM2022015) and Open Program of Key Laboratory of Intelligent Pharmacy and Individualized Therapy of Huzhou & Changxing Anti-cancer Association (No. HZKF-20230205).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Joint Commission International, Joint Commission on Accreditation of Healthcare Organizations. *Joint Commission International Accreditation Standards for Hospitals*. 7th ed. Oak Brook, IL: Joint Commission Resources; 2020.
2. Goldspiel B, Hoffman JM, Griffith NL, et al. ASHP guidelines on preventing medication errors with chemotherapy and biotherapy. *Am J Health Syst Pharm*. 2015;72(8):e6–e35. doi:10.2146/sp150001
3. Dhamija M, Kapoor G, Juneja A. Infusional chemotherapy and medication errors in a tertiary care pediatric cancer unit in a resource-limited setting. *J Pediatr Hematol Oncol*. 2014;36(7):e412–e415. doi:10.1097/MPH.0000000000000044
4. Zhu LL, Li W, Song P, Zhou Q. Injection device-related risk management toward safe administration of medications: experience in a university teaching hospital in The People's Republic of China. *Ther Clin Risk Manag*. 2014;10:165–172. doi:10.2147/TCRM.S59199
5. Park J, You SB, Kim H, et al. Experience of nurses with intravenous fluid monitoring for patient safety: a qualitative descriptive study. *Risk Manag Healthc Policy*. 2022;15:1783–1793. doi:10.2147/RMHP.S374563
6. Garcia-Alonso A. Improving the chemotherapy process and service to cancer patients. *Risk Manag Healthc Policy*. 2011;4:41–45. doi:10.2147/RMHP.S16059
7. Hiraga S, Arita N, Ohnishi T, et al. Rapid infusion of high-dose methotrexate resulting in enhanced penetration into cerebrospinal fluid and intensified tumor response in primary central nervous system lymphomas. *J Neurosurg*. 1999;91(2):221–230. doi:10.3171/jns.1999.91.2.0221
8. Piedbois P, Rougier P; Meta-analysis Group In Cancer. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. *J Clin Oncol*. 1998;16:301–308. doi:10.1200/JCO.1998.16.1.301
9. Hoshino S, Yamashita Y, Maekawa T, Shirakusa T. Effects on DNA and RNA after the administration of two different schedules of 5-fluorouracil in colorectal cancer patients. *Cancer Chemother Pharmacol*. 2005;56(6):648–652. doi:10.1007/s00280-004-0985-9
10. Zhou J, Meng R, Sui XH, Meng L, Yang BF. Effects of arsenic trioxide administration styles on leukocytosis. *Chin Med Sci J*. 2006;21:111–114.
11. Pasternak AL, Link NA, Richardson CM, Rose PG. Effect of prophylactic extended-infusion carboplatin on incidence of hypersensitivity reactions in patients with ovarian, fallopian tube, or peritoneal carcinomas. *Pharmacotherapy*. 2016;36:723–730. doi:10.1002/phar.1769
12. O'Cearbhaill R, Zhou Q, Iasonos A, et al. The prophylactic conversion to an extended infusion schedule and use of premedication to prevent hypersensitivity reactions in ovarian cancer patients during carboplatin retreatment. *Gynecol Oncol*. 2010;116:326–331. doi:10.1016/j.ygyno.2009.10.070
13. LaVigne K, Hyman DM, Zhou QC, et al. A randomized trial of prophylactic extended carboplatin infusion to reduce hypersensitivity reactions in recurrent ovarian cancer. *Int J Gynecol Cancer*. 2018;28(6):1176–1182. doi:10.1097/IGC.0000000000001280
14. Petrioli R, Pascucci A, Francini E, et al. Neurotoxicity of FOLFOX-4 as adjuvant treatment for patients with colon and gastric cancer: a randomized study of two different schedules of oxaliplatin. *Cancer Chemother Pharmacol*. 2008;61:105–111. doi:10.1007/s00280-007-0454-3.
15. Huynh T, Crozier N, Anselmo L. Safety outcomes of rapid- versus standard-infusion rate oxaliplatin. *J Oncol Pharm Pract*. 2023;1:10781552231192007. doi:10.1177/10781552231192007.
16. Thigpen JT, Blessing JA, DiSaia PJ, Fowler WC Jr, Hatch KD. A randomized comparison of a rapid versus prolonged (24 hr) infusion of cisplatin in therapy of squamous cell carcinoma of the uterine cervix: a Gynecologic Oncology Group study. *Gynecol Oncol*. 1989;32(2):198–202. doi:10.1016/s0090-8258(89)80033-2
17. Mense ES, Smit AAJ, Crul M, Franssen EJF. The effect of rapid infusion of cisplatin on nephrotoxicity in patients with lung carcinoma. *J Clin Pharm Ther*. 2019;44:249–257. doi:10.1111/jcpt.12781
18. Shapira J, Gotfried M, Lishner M, Ravid M. Reduced cardiotoxicity of doxorubicin by a 6-hour infusion regimen. A prospective randomized evaluation. *Cancer*. 1990;65(4):870–873. doi:10.1002/1097-0142(19900215)65:4<870::AID-CNCR2820650407>3.0.CO;2-D
19. Cranmer LD, Hess LM, Sugihara T, Muntz HG. Cardiac events among patients with sarcoma treated with doxorubicin by method of infusion: a real-world database study. *Cancer Rep*. 2023;6:e1681. doi:10.1002/cnr2.1681

20. Cranmer LD, Lu Y, Heise RS, et al. Bolus versus continuous intravenous delivery of doxorubicin in soft-tissue sarcomas: post hoc analysis of a prospective randomized trial (SARC021/TH CR-406). *Clin Cancer Res*. 2023;29(6):1068–1076. doi:10.1158/1078-0432.CCR-22-1564
21. Perreault S, Baker J, Medoff E, et al. Infusion reactions are common after high-dose carmustine in BEAM chemotherapy and are not reduced by lengthening the time of administration. *Support Care Cancer*. 2017;25(1):205–208. doi:10.1007/s00520-016-3399-4
22. RxList [homepage on the Internet]. BICNU; 2021. Available from: https://www.rxlist.com/bicnu-drug.htm#indications. Accessed September 24, 2023.
23. RxList [homepage on the Internet]. Gemzar; 2018. Available from: https://www.rxlist.com/gemzar-drug.htm#dosage. Accessed September 23, 2023.
24. Khatri A, Williams BW, Fisher J. SLC28A3 genotype and gemcitabine rate of infusion affect dFdCTP metabolite disposition in patients with solid tumours. *Br J Cancer*. 2014;110(2):304–312. doi:10.1038/bjc.2013.738
25. Cappuzzo F, Novello S, De Marinis F, et al. A randomized phase II trial evaluating standard (50 mg/min) versus low (10 mg/min) infusion duration of gemcitabine as first-line treatment in advanced non-small-cell lung cancer patients who are not eligible for platinum-based chemotherapy. *Lung Cancer*. 2006;52:319–325. doi:10.1016/j.lungcan.2006.03.004
26. Kosmas C, Kallistratos MS, Kopterides P, et al. Cardiotoxicity of fluoropyrimidines in different schedules of administration: a prospective study. *J Cancer Res Clin Oncol*. 2008;134(1):75–82. doi:10.1007/s00432-007-0250-9
27. Lévy E, Piedbois P; Meta-Analysis Group In Cancer. Toxicity of fluorouracil in patients with advanced colorectal cancer: effect of administration schedule and prognostic factors. *J Clin Oncol*. 1998;16:3537–3541. doi:10.1200/JCO.1998.16.11.3537
28. van Zuylen L, Gianni L, Verweij J, et al. Inter-relationships of paclitaxel disposition, infusion duration and cremophor EL kinetics in cancer patients. *Anticancer Drugs*. 2000;11(5):331–337. doi:10.1097/00001813-200006000-00003
29. Jennens R, Rischin D, Yuen K, Toner G, Millward M. Comparison of neutropenia in a randomized, crossover trial of 3-, 6-, and 24-h infusions of paclitaxel. *Gynecol Oncol*. 2003;91(1):190–193. doi:10.1016/s0090-8258(03)00459-1
30. Gelderblom H, Mross K, ten Tije AJ, et al. Comparative pharmacokinetics of unbound paclitaxel during 1- and 3-hour infusions. *J Clin Oncol*. 2002;20(2):574–581. doi:10.1200/JCO.2002.20.2.574
31. Taira K, Okazaki S, Akiyoshi K, et al. Short bevacizumab infusion as an effective and safe treatment for colorectal cancer. *Mol Clin Oncol*. 2022;17(3):139. doi:10.3892/mco.2022.2572
32. Yanmaz MT, Guner SI, Satılmıs B, Akyol H, Aydın MA. Thirty-minutes infusion rate is safe enough for bevacizumab; no need for initial prolong infusion. *Med Oncol*. 2014;31(11):276. doi:10.1007/s12032-014-0276-1
33. Makris G, Kantzioura A, Beredima M, Karampola M, Emmanouilides C. Feasibility of rapid infusion of the initial dose of bevacizumab in patients with cancer. *J BUON*. 2015;20(3):923–927.
34. RxList [homepage on the Internet]. Rituxan; 2021. Available from: http://www.rxlist.com/rituxan-drug/indications-dosage.htm. Accessed September 23, 2023.
35. Swan JT, Zaghloul HA, Cox JE, Murillo JR Jr. Use of a pharmacy protocol to convert standard rituximab infusions to rapid infusion shortens outpatient infusion clinic visits. *Pharmacotherapy*. 2014;34(7):686–694. doi:10.1002/phar.1420
36. Moore DC, Gebru T, Plesca D. Evaluation of a pharmacist-driven rapid infusion rituximab conversion protocol at a multisite cancer center. *J Oncol Pharm Pract*. 2021;27(8):1914–1918. doi:10.1177/1078155220977898
37. Stakiw J, Kodad S, LeBlanc R, et al. A Phase II, Open-label study of an accelerated infusion rate of daratumumab in patients with relapsed and refractory multiple myeloma. *Clin Lymphoma Myeloma Leuk*. 2023;23(7):484–490. doi:10.1016/j.clml.2023.03.006
38. Hamadeh IS, Reese ES, Arnall JR, et al. Safety and cost benefits of the rapid daratumumab infusion protocol. *Clin Lymphoma Myeloma Leuk*. 2020;20(8):526–532.e1. doi:10.1016/j.clml.2020.02.014
39. Gao L, Lau YK, Wei R, et al. Evaluating clinical impact of a shortened infusion duration for ramucirumab: a model-based approach. *Cancer Chemother Pharmacol*. 2021;87(5):635–645. doi:10.1007/s00280-020-04223-9
40. RxList [homepage on the Internet]. Cyramza; 2022. Available from: https://www.rxlist.com/cyramza-drug.htm#dosage. Accessed September 24, 2023.
41. Yao D, Shen H, Huang J, Yuan Y, Dai H. Influence of different drug delivery methods for Endostar combined with a gemcitabine/cisplatin regimen in locally advanced or metastatic lung squamous cell carcinoma: a retrospective observational study. *Medicine*. 2018;97(32):e11822. doi:10.1097/MD.0000000000011822
42. RxList [homepage on the Internet]. Paclitaxel; 2022. Available from: https://www.rxlist.com/paclitaxel/generic-drug.htm. Accessed September 24, 2023.
43. RxList [homepage on the Internet]. Rituxan; 2021. Available from: https://www.rxlist.com/rituxan-drug.htm#dosage. Accessed September 24, 2023.
44. Mikkelsen TS, Sparreboom A, Cheng C, et al. Shortening infusion time for high-dose methotrexate alters antileukemic effects: a randomized prospective clinical trial. *J Clin Oncol*. 2011;29(13):1771–1778. doi:10.1200/JCO.2010.32.5340
45. Sao LR, Young FD, Otani IM, Castells MC. Hypersensitivity reactions to platinum agents and taxanes. *Clin Rev Allergy Immunol*. 2022;62:432–448. doi:10.1007/s12016-021-08877-y
46. O'Malley DM, Vetter MH, Cohn DE, Khan A, Hays JL. Outpatient desensitization in selected patients with platinum hypersensitivity reactions. *Gynecol Oncol*. 2017;145(3):603–610. doi:10.1016/j.ygyno.2017.03.015
47. RxList [homepage on the Internet]. Abraxane; 2021. Available from: https://www.rxlist.com/abraxane-drug.htm. Accessed September 24, 2023.
48. Dranitsaris G, Yu B, Wang L. Abraxane® versus Taxol® for patients with advanced breast cancer: a prospective time and motion analysis from a Chinese health care perspective. *J Oncol Pharm Pract*. 2016;22(2):205–211. doi:10.1177/1078155214556008
49. RxList [homepage on the Internet]. DOXIL; 2022. Available from: https://www.rxlist.com/doxil-drug.htm. Accessed September 23, 2023.
50. Metharom E, Galettis P, Manners S, et al. The pharmacological advantage of prolonged dose rate gemcitabine is restricted to patients with variant alleles of cytidine deaminase c.79A>C. *Asia Pac J Clin Oncol*. 2011;7(1):65–74. doi:10.1111/j.1743-7563.2010.01354.x
51. Ramsey LB, Panetta JC, Smith C, et al. Genome-wide study of methotrexate clearance replicates SLCO1B1. *Blood*. 2013;121(6):898–904. doi:10.1182/blood-2012-08-452839