

Oral Versus Intravenous Chemotherapy in COVID-19 Epidemic

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Abstract: The novel coronavirus has a significant impact on the routine clinical practice for cancer patients in China since December 2019. During the epidemic in mainland China, especially Wuhan, the intravenous chemotherapies of cancer patients were considerably delayed. Up to now, cancer patients throughout the world directly encounter similar obstacles. For patients who have the right to choose chemotherapeutic regimens with different administration routes, oral drugs can be considered to be applied. In this mini-review, oral chemotherapeutic drugs were compared with intravenous drugs in seven types of tumors. Accordingly, we intended to provide useful suggestions for clinicians to balance the benefits and risks of oral against intravenous chemotherapies and to choose properly substituted oral chemotherapeutic regimens for cancer patients amid the coronavirus disease 2019 (COVID-19) pandemic.

Keywords: Oral chemotherapy; Intravenous chemotherapy; Coronavirus disease.

Introduction

Intravenous chemotherapy is the mainstay treatment of cancer patients. However, patients receiving intravenous chemotherapy are required to be treated within hospitals. The development of oral chemotherapy has brought great convenience to patients. With the spread of coronavirus disease 2019 (COVID-19), clinicians are willing to choose oral chemotherapy or oral drugs-contained chemotherapeutic regimens. If cancer patients have the choice, they may prefer oral chemotherapy to intravenous strategies since oral regimens are more acceptable. In addition, the length of hospital stay will be shortened, and subsequently, the risk of COVID-19 infection and spread will be decreased. In addition, feasibilities and safety profiles should also be brought to the forefront.

1. Oral etoposide in small-cell lung cancer

Small-cell lung cancer (SCLC) is a highly malignant cancer. The combination of cisplatin and etoposide chemotherapy is the standard-of-care for both limited and extensive stage diseases^[1]. In a population-based study, the authors comprehensively compared the efficacy and safety of oral etoposide with intravenous etoposide^[2]. Patients in both groups, including limited-stage SCLC (17.5 versus 17.9 months) and extensive-stage SCLC (8.7 versus

9.7 months), showed similar overall survivals (OSs)^[2]. Therefore, in the circumstance of COVID-19, oral etoposide plus nedaplatin or lobaplatin could be an alternative therapeutic option for treatment-naïve patients with SCLC.

However, local recurrence and distant metastasis within one year are the basic characteristics of SCLC patients after receiving first-line treatment^[3]. A study reported by Gervais provided an oral chemotherapeutic strategy for patients with advanced SCLC^[4]. The oral chemotherapy consisted of lomustine, cyclophosphamide, and etoposide, compared with intravenous cyclophosphamide, doxorubicin, and vincristine chemotherapy. The median OS was 6.1 months in the oral arm versus 5.8 months in the intravenous arm. The oral chemotherapy had a disease control rate (DCR) of 61.5% versus 48.5% for intravenous chemotherapy. Moreover, both strategies showed no significant differences in terms of adverse events. In the second-line treatment for patients with SCLC, although a combination of oral lomustine, cyclophosphamide, and etoposide might be an effective treatment in preventing disease progression for SCLC during the COVID-19 epidemic, oral chemotherapy might also be applied with great cautions.

2. Oral vinorelbine in non-small-cell lung cancer

Platinum-based chemotherapies or chemoradiotherapies are the backbones of the treatment for non-small-cell lung cancer (NSCLC). Except targeting therapeutic drugs, such as tyrosine kinase inhibitors, extremely few oral chemotherapies have been recommended to patients with NSCLC. One of the frequently used oral chemotherapeutic drugs in NSCLC is vinorelbine (VRL), which is a semi-synthetic vinca alkaloid^[5].

For resected NSCLC patients, VRL plus cisplatin is an adjuvant chemotherapeutic strategy. Sorensen et al. assessed the

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survival outcomes in patients treated with cisplatin plus oral VRL or intravenous VRL^[6]. Even the results were not statistically significant. Oral VRL showed a worse median OS (58.5 months versus 79.5 months) and a shorter disease-free survival (DFS) (22.6 months versus 45.6 months) compared to intravenous VRL. Therefore, oral VRL combined with cisplatin, as adjuvant chemotherapy, is not recommended to resected NSCLC patients.

For unresectable or advanced NSCLC patients, oral VRL has also been studied. In Yang's study, the efficacy and tolerability were evaluated to compare oral VRL plus cisplatin with intravenous VRL plus cisplatin in patients with previously untreated unresectable or advanced NSCLC^[7]. The median OS was 16.1 months in the oral arm versus 19.0 months in the intravenous arm, while the median progression-free survival (PFS) was 4.6 months in the oral arm versus 4.9 months in the intravenous arm. For toxicities, oral VRL had a lower incidence of febrile neutropenia than intravenous VRL (6.1% versus 9.2%).

Even the oral VRL could be a substitute for intravenous VRL in the first-line treatment of advanced NSCLC, however, it might still be difficult for a clinician to control the disease progression of NSCLC depending on the existing oral chemotherapeutic drugs. Thus, for patients with NSCLC without driving gene mutations, intravenous chemotherapy should be the best therapeutic strategy during the epidemic.

3. Oral S-1 and DHP107 in gastric cancer

For gastric cancer (GC) patients, the combination of fluoropyrimidine and platinum is the standard strategy. In 2017, Ajani et al. compared oral S-1 plus cisplatin and intravenous 5-fluorouracil (5-FU) plus cisplatin in untreated diffuse GC patients and showed an objective response rate (ORR) of 34.7% in oral S-1 plus cisplatin group versus 19.8% in intravenous 5-FU plus cisplatin group^[8]. Thus, in the first-line treatment for GC patients, although platinum drugs are unavoidable, intravenous 5-FU could be considered to be replaced by oral S-1.

In the second-line treatment for patients with advanced GC, paclitaxel has been widely used^[8,9]. An oral formulation composed of lipid ingredients and paclitaxel is DHP107, which is systemically absorbed without the need for P-glycoprotein inhibitors^[10]. Kang's study has illustrated the promising benefit of DHP107 on gastric cancer^[11]. The survival outcomes of advanced GC patients treated oral DHP107 were non-inferior to those treated with intravenous paclitaxel (OS: hazard ratio [HR] 1.04, 95% confidence interval [CI] 0.76-1.41; PFS: HR 0.85, 95% CI 0.64-1.13). The ORRs were 17.8% for DHP107 and 25.4% for paclitaxel.

Accordingly, oral chemotherapeutic drugs, comprising S-1 and DHP107, could be an effective treatment for GC patients when they are inconvenient to receive hospitalized chemotherapies during the spread of COVID-19.

4. Oral capecitabine and UFT in colorectal cancer

The mainstay of systematic chemotherapy for advanced colorectal cancer (CRC) is the intravenous administration of 5-FU^[12-14]. 5-FU is commonly used in combination with oxaliplatin or irinotecan^[15,16]. Oral fluoropyrimidines have been developed to

overcome challenges associated with intravenous 5-FU. Two meta-analyses have shown us comprehensive comparisons^[17,18].

In 2017, Chionh et al.^[17] indicated that OS (HR 0.92, 95% CI 0.84-1.00) and DFS (HR 0.93, 95% CI 0.87-1.00) did not significantly differ between the CRC patients with oral versus intravenous fluoropyrimidines, who were treated with curative intent with neoadjuvant and/or adjuvant chemotherapy. The neoadjuvant and/or adjuvant patients who received oral fluoropyrimidines might experience less grade 3 or more adverse events (odds ratio [OR] 0.82, 95% CI 0.74-0.90). However, oral fluoropyrimidines could exert higher incidences of grade 3 or more hand-foot syndrome (OR 4.59, 95% CI 2.97-7.10). When advanced CRC patients were treated with palliative chemotherapy, oral fluoropyrimidines were inferior to intravenous fluoropyrimidines in PFS (HR 1.06, 95% CI 1.02-1.11) but not OS (HR 1.02, 95% CI 0.99-1.05) and ORR (OR 0.98, 0.90-1.06). Similarly, advanced CRC patients treated with oral fluoropyrimidines had fewer incidences of grade 3 or more adverse events (OR 0.83, 95% CI 0.74-0.94). But oral treatment strategy induced more grade 3 or more diarrhea (OR 1.66, 95% CI 1.50-1.84) and hand-foot syndrome (OR 3.92, 95% CI 2.84-5.43).

Capecitabine is the most widely used oral fluoropyrimidine in CRC patients. In 2018, Wu et al.^[18] systematically compared the efficacy and safety of capecitabine with intravenous 5-FU in advanced CRC. In the analysis, oral capecitabine had a 10% decrease in ORR compared with intravenous 5-FU (OR 0.90, 95% CI 0.83-0.98). However, no significant differences had been observed in OS (HR 1.00, 95% CI 0.94-1.06) and DFS (HR 0.96, 95% CI 0.85-1.08) between the two treatment modalities. For adverse events, Wu demonstrated that intravenous 5-FU had an improved safety profile against oral capecitabine.

Another oral fluoropyrimidine formulation, UFT, combines uracil and tegafur in a fixed molar ratio of 4:1. In the trial conducted by Borner et al., advanced CRC patients who received oral UFT plus leucovorin had a DCR of 88.2% versus 71.4% in the intravenous 5-FU plus leucovorin group. In addition, advanced CRC patients enrolled in the study experienced less hematological toxicities with oral UFT plus leucovorin^[19].

Based on guidelines for CRC, capecitabine monotherapy could be suggested as an alternative option for CRC patients, especially during the COVID-19 epidemic. Moreover, patients with CRC prefer oral over intravenous chemotherapy treatment, regardless of whether they are treated with capecitabine or UFT. Convenience and safety are the most critical factors affecting clinicians' and patients' choices.

5. Oral vinorelbine plus capecitabine in breast cancer

For patients with estrogen receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer (BC), oral chemotherapy is preferred other than intravenous chemotherapy. However, the therapeutic strategies contained both oral and intravenous drugs^[20]. Up to now, there is still an absence of all-oral chemotherapy for early-stage BC patients.

The all-oral combination of vinorelbine and capecitabine appears to be an effective and well-tolerated treatment for advanced breast cancer^[21]. In 2012, Strada et al. found that both oral vinorelbine plus capecitabine and intravenous vinorelbine plus

capecitabine achieved high DCRs (76.0% versus 73.2%) as a first-line treatment of advanced HER2-negative breast cancer. Additionally, the oral combination therapy showed a benefit on quality of life^[22]. In 2016, Cinieri et al. compared first-line oral vinorelbine plus capecitabine with gemcitabine plus paclitaxel and gemcitabine plus docetaxel in advanced HER2-negative breast cancer. The DCRs were 73.5% with oral vinorelbine plus capecitabine, 78.0% with gemcitabine plus paclitaxel, and 80.0% with gemcitabine plus docetaxel^[23]. Although the oral chemotherapy indicated a slightly lower DCR than intravenous chemotherapy, the oral strategy, vinorelbine plus capecitabine, could be an active first-line chemotherapy regimen for advanced HER2-negative breast cancer patients in the COVID-19 outbreak.

6. Oral RIF in Acute promyelocytic leukemia

Acute promyelocytic leukemia (APL) is a highly curable hematological tumor. The standard treatment drugs are arsenic (ATO) and all-trans retinoic acid (ATRA)^[24]. ATRA is administered by an oral pathway, but ATO must be intravenously infused in a hospital setting. The Realgar-Indigo naturalis formula (RIF) is an oral tetra-arsenic tetra-sulfide (As_4S_4) with a complete response (CR) rate of 96.7% and a tolerable safety profile^[25,26]. To demonstrate whether oral arsenic RIF was non-inferior to intravenous ATO, Zhu et al. conducted two randomized controlled studies comparing the benefits and risks of oral RIF with intravenous ATO in the treatment-naïve APL patients^[27,28]. Both studies showed that the oral RIF provided outcomes similar to that exerted with intra-venous ATO (CR rate: 99.1-100% versus 94-97.2%; 2-year survival rate: 100% versus 94%; 3-year survival rate: 99.1% versus 96.6%). Thus, oral RIF plus ATRA might be suggested as an ideal treatment option for APL patients during the spread of coronavi-rus disease (COVID).

7. Oral etoposide combined with apatinib Ovarian Cancer

Intravenous chemotherapeutics are the main treatment strategies of ovarian cancer (OC) patients. Nevertheless, patients with OC prefer oral to intravenous chemotherapy either^[29].

Oral etoposide has been used in OC patients. For patients with platinum-resistant/refractory OC, oral etoposide combined with intravenous irinotecan showed a moderated response rates with a PFS of 4.1 months and an OS of 11.9 months. However, three of the enrolled 61 patients who suffered treatment-related death were reported. Therefore, the authors did not recommend this strategy outside because of adverse events^[30].

Fortunately, the combination of oral etoposide with apatinib showed a promising efficacy with a 54% ORR and a manageable safety profile^[31]. Thus, oral etoposide plus apatinib might be a potential regimen for previously platinum treated OC patients amid the epidemic.

Conclusions

The existing oral chemotherapeutic drugs are hard to achieve total coverage of all tumor types. Moreover, intravenous

chemothera-pies could not be fully replaced by oral treatment strategies.

During the epidemic of COVID-19, all-oral chemotherapies alone can only provide a certain tumor control effect for patients with several types of cancer, like gastric cancer or colorectal cancer. It should be noted that, although there is no considerable difference in adverse events between oral chemotherapy and intravenous chemotherapy, toxicities still exist. It should be challenging to treat the toxicities at home, which may threaten the life of patients. More safe and efficient oral drugs and chemotherapeutic strategies are needed to be explored in future studies. For hospitals, strict internal management and prevention measures must be the guarantee for cancer patients to receive timely treatment.

Abbreviations

APL, Acute promyelocytic leukemia; As_4S_4 , tetra-arsenic tetra-sulfide; ATO, arsenic; ATRA, all-trans retinoic acid; BC, breast cancer; COVID-19, coronavirus disease 2019; CR, complete response; CRC, colorectal cancer; DCR, disease control rate; DFS, disease-free survival; GC, gastric cancer; HR, hazard ratio; NS-CLC, non-small-cell lung cancer; OC: ovarian cancer; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RIF, Realgar-Indigo naturalis formula; SCLC, Small-cell lung cancer; VRL, vinorelbine; 5-FU, 5-fluorouracil.

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Conflict of interest

The author declared no potential conflicts of interest.

Authors' contributions

Study design: BCW; Article search: BCW and BYX; Manuscript writing and edition: BCW and BYX.

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