Cancer Care Ontario

Guidance on the Substitution of Systemic Therapy Agents

A project developed by the Evidence-informed Working Group and Systemic Treatment-QBP of Cancer Care Ontario for circulation to Regional Cancer Programs. External review was conducted by representatives of the University Health Network and Southlake Regional Health Centre.

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Version 1

Methods/Approach:

In 2015, CCO assembled an Evidence-informed Working Group consisting of clinical experts to accomplish three primary objectives:

1. Develop a formal definition of evidence-informed practice
2. Develop criteria to determine if a regimen is evidence-informed
3. Provide guidance on issues such as dose or schedule modifications and drug substitutions to evidence-informed regimens

In the first phase of the Evidence-informed Working Group, the first objective was completed in the document entitled “Guidance to Disease Site Leads and Others Involved in Recommending New Drugs and Regimens for Funding Through Cancer Care Ontario’s Systemic Treatment – Quality-Based Program”. The second objective was completed through the development of a new ST-QBP Drug/Regimen Request Form, which includes an assessment checklist.

The Evidence-informed Working Group was re-constituted for a second phase and has completed the third objective – this document. The guidance herein is based on evidence to the extent possible (including use of Program in Evidence-Based Care (PEBC) clinical guidelines), but where evidence does not exist, clinical expert opinion has been utilized.

Introduction:

The medical decision to substitute one systemic therapy agent for another may be undertaken for a variety of reasons. This document is meant to describe those situations in which one chemotherapy drug is used for another of a similar class and mechanism of action. The two most common reasons for drug substitution include convenience for the patient (ie. oral versus

intravenous administration) and avoidance of toxicities that would aggravate a pre-existing condition (eg. substitution of a less neurotoxic drug in a patient with diabetic neuropathy). The decision to substitute one chemotherapy drug for another should always be undertaken in the best interests of the patient and not compromise treatment outcomes. The guiding principles which follow can be applied to both intravenous and oral drug substitutions. Examples of both types of drug substitutions are provided below; however, it must be noted that intravenous drug substitutions are managed through the Systemic Treatment-QBP (ST-QBP), whereas oral drug substitutions require discussion with the Ministry of Health and Long-Term Care (MOHLTC). Nonetheless, drug substitutions, be they oral or intravenous agents, should be guided by the same principles as articulated below.

Guiding Principles:

1. To the extent possible, decisions concerning drug substitutions should be informed by evidence and generally should be disease-site specific. This guidance applies to the choice of the initial therapy for a patient. It is not meant to guide practice when toxicities are encountered during treatment and drug substitution is necessary because of organ injury or patient symptoms.
2. If a systemic therapy regimen has been shown to be beneficial when used with curative intent, drug substitution should not be undertaken unless there is either evidence from one or more randomized trials that drug substitution will not adversely affect the outcome, or drug substitution is necessitated by drug toxicity, which may be ameliorated by substitution.
3. If the systemic therapy is being administered with palliative intent, the level of evidence for drug substitution does not need to be as rigorous and quality of life (QOL) should be an important consideration. The option for drug substitution should take into account factors such as organ function, anticipated toxicity, patient convenience and cost to the health care system. Ideally, drug substitution in this situation should still be recommended by disease site experts in clinical practice guidelines.

Brief summaries are provided below of the evidence for some of the most common drug substitutions for specific diseases and clinical circumstances. These disease-site specific summaries are meant to provide guidance on how to approach drug substitutions and do not represent an exhaustive list. Facilities should submit drug substitutions using the unique regimen code developed by CCO for the substituted drug. The unique regimen codes for substituted drugs are listed on CCO's evidence-informed regimens list as well as in iPort. Except where noted, the examples below are listed as evidence-informed.

Examples of Intravenous Drug Substitution

Substitution of Carboplatin for Cisplatin

The following are disease-site specific examples that illustrate the recommendation to use the regimen that showed the best survival outcomes in a randomized clinical trial when the regimen is used with curative intent unless organ dysfunction or toxicity on treatment preclude its use and the substitution of a less toxic agent when palliation is the primary goal of therapy.

Non-small Cell Lung Cancer:

Cisplatin in combination with vinorelbine has been demonstrated to increase the proportion of early stage resected non-small cell lung cancer (NSCLC) patients alive at 5 years. It is, therefore, recommended that carboplatin not be substituted for cisplatin when adjuvant chemotherapy is administered in this potentially curative situation. In this example, the clinical trial was done using cisplatin and the adjuvant use of the regimen led to a higher percentage of patients being alive at 5 years.

The treatment of locally advanced and metastatic NSCLC is currently non-curative. CCO guideline EBS 7-10 version 3 indicates that “platinum-based two-drug combinations were slightly superior to nonplatinum-based combinations for overall survival”, and that cisplatin-based doublet therapy was slightly superior to carboplatin-based therapy for survival. However, given the poor prognosis of this patient population, the guideline also states that “individual patient decisions should reflect the balance among improved survival, increased toxicity, and patient preference” and carboplatin can be substituted if patients experience significant toxicities with the cisplatin-based therapy. In this example, although data suggests that cisplatin may be a little more effective than carboplatin-based regimens, the benefit is small, cisplatin is more toxic than carboplatin and the setting is palliative.

Small Cell Lung Cancer:

Although small cell lung cancer (SCLC) is generally incurable, patients with limited stage disease have a 20% chance of 5 year survival. CCO guideline EBS 7-13-1 version 2 states that etoposide-cisplatin is “preferred” and that there is “insufficient data from clinical trials to support the substitution of carboplatin in patients with limited SCLC being treated with curative intent”. In the setting of extensive stage disease, where cure is not possible and QOL is an important consideration, carboplatin may be substituted for cisplatin if there is significant drug-related toxicity. In SCLC, patients with limited disease have a chance for long-term survival, so the recommendation is to use the drug regimen (etoposide-cisplatin) that has provided the greatest benefit. In extensive disease, the goal is palliation so carboplatin may be substituted if cisplatin is causing excessive toxicity.

Ovarian Cancer:

The use of platinum-based therapy in the systemic therapy of ovarian cancer is commonly not curative. In the CCO guideline on the optimal chemotherapy for recurrent ovarian cancer EBS 4-3 version 4 recommended systemic therapy is listed as including carboplatin and paclitaxel, carboplatin and gemcitabine or carboplatin and pegylated liposomal doxorubicin. If combination platinum-based chemotherapy is contraindicated, then a single platinum agent can be considered. The guideline specifically notes that "carboplatin has demonstrated efficacy across trials and has a manageable toxicity profile". In the setting of advanced ovarian cancer, cure is not possible so attention to the patient's quality of life is the justification for the use of carboplatin over cisplatin.

Head and Neck Cancer:

CCO guideline EBS 5-11 on the postoperative management of advanced squamous cell cancer of the head and neck recommends adjuvant chemo-radiotherapy as an effective treatment approach to improve control and survival outcomes for those patients at a high risk of recurrence who are willing and deemed able to tolerate the addition of chemotherapy to radiotherapy. Specifically, the guideline states the role of chemotherapy is most clear for its concomitant use with postoperative or radical radiation therapy. This benefit was more profound with platinum-based chemotherapy, and the most robust evidence is for cisplatin. The use of postoperative adjuvant chemo-radiotherapy regimen consisting of high-dose cisplatin 100 mg/m^2 administered IV every 21 days for three cycles concurrently with standard doses of conventionally fractionated radiotherapy was most commonly studied but alternative cisplatin schedules (optimal doses of at least 40 mg/m^2 per week) may be quite reasonable. Cisplatin is an effective radiosensitizer and studies indicate that cisplatin with radiotherapy improves the potential for long-term survival. As the goal of chemo-radiotherapy is cure, substitution of carboplatin for cisplatin should not be routinely undertaken.

For patients with newly diagnosed locally advanced squamous cell or undifferentiated nasopharyngeal cancer (stage III or IV), CCO guideline EBS 5-7 version 2 recommends that cisplatin-based concurrent chemo-radiotherapy be routinely offered, as four trials with cisplatin-based concurrent chemo-radiotherapy showed a significant overall survival difference vs. radiotherapy alone. As the goal of the combined modality treatment is cure and the evidence was generated using cisplatin-based concurrent chemo-radiotherapy, substitution of carboplatin for cisplatin should not be routinely undertaken.

Substitution of Docetaxel for Paclitaxel

Paclitaxel is commonly used in the treatment of gynecological malignancies as well as breast and lung cancers amongst other cancers. Hypersensitivity reactions (HSR) to paclitaxel, including hypertension, bronchospasm, breathlessness and cutaneous flushing, occur within less than 10% of paclitaxel infusions and have been attributed to the Cremophor EI diluent.

Typically such reactions are managed with the use of a combination of H1 and H2 blockers and corticosteroids. Premedication with these agents or the use of a longer infusion can prevent subsequent HSRs in most patients. An alternative strategy is to substitute docetaxel for paclitaxel. Occasionally, patients will also have a HSR to docetaxel suggesting that at least in some patients, the allergic reaction is linked to the taxane moiety.

The combination of paclitaxel and carboplatin is commonly used in the management of advanced ovarian cancer and can result in severe neuropathy. The medical literature indicates that substituting docetaxel for paclitaxel can result in a decrease or resolution of established neurotoxicity.

Examples of Oral Drug Substitution for Intravenous Drugs

Substitution of Oral Capecitabine for Intravenous 5-fluorouracil

Fluorouracil (FU) is an antimetabolite with activity against a range of neoplasms, including cancers of the breast, esophagus, larynx, and gastrointestinal and genitourinary tracts. Systemic toxicity, including neutropenia, stomatitis, and diarrhea, often occur due to cytotoxic non-selectivity. Capecitabine is a prodrug that is enzymatically converted to 5-fluorouracil (5-FU) in the body and was developed with the goal of improving tolerability and intra-tumour drug concentrations through tumour-specific conversion to the active drug. Capecitabine is contraindicated in the face of severe hepatic impairment or severe renal impairment.

CCO is currently working with our tumour-specific drug advisory committees for the gastrointestinal and head & neck disease sites to add the substitution of capecitabine for 5-FU to the evidence-informed regimens list.

Colorectal Cancer:

CCO guideline EBS 2-29 version 2 recommends that patients with completely resected stage III colon cancer should be offered adjuvant chemotherapy but that the choice of treatment should depend on factors such as patient suitability and preference. Options include FOLFOX, FLOX, XELOX, capecitabine, or 5-fluorouracil (5-FU) + leucovorin (LV). The guideline notes that oral capecitabine has equivalent efficacy to intravenous bolus 5-FU/LV; however, capecitabine results in significantly less diarrhea, stomatitis, neutropenia, nausea/vomiting, and alopecia but significantly more hand-foot syndrome when compared with bolus 5-FU/LV.

CCO guideline EBS 2-15 on the first-line treatment of metastatic colorectal cancer, states that the standard combination chemotherapy consists of infusional 5-FU plus LV with either irinotecan or oxaliplatin. This guideline also indicates that if infusional therapy with 5-FU plus LV is not reasonable, then treatment using oral capecitabine is appropriate. The decision to use capecitabine may be influenced by its toxicity and/or convenience to the patients.

Conclusion:

The examples described above coupled with the guiding principles should assist clinicians with making evidence-informed decisions about drug substitutions that may be required in their practices.

Contact:

Any questions regarding the content of this guidance document can be sent to STFM@cancercare.on.ca.