The Use of Capecitabine in Cancer: Management of The Hand Foot Syndrome

Aru W Sudoyo

INTRODUCTION

Colorectal cancer (CRC) ranks among the 10 most common cancers in the world, including Indonesia. It is the most environmentally-related cancer and in this country sporadic CRC affects 35.2% of people below 40 years old, as compared to only 3% in developed countries, making it an increasingly important health issue as the disease deprives the country of resources and productivity.

Surgery is the main treatment modality, but more than 30% of CRC present already with metastasis – whereas another 30% will eventually develop the condition – so chemotherapy will eventually have to be considered at one point. In the last few years, the development of chemotherapy of CRC has seen more new drugs than other types of cancers. The drug 5-fluorouracil (5-FU) has been and is still the backbone of the cytostatic regimen, further enhanced with folinic acid (leucovorin) and in recent years with the addition of irinotecan and oxaliplatin. Several regimens were used in various institutions, i.e., the AIO, Roswell Park, and the de Gramont regimen, all of them involving the intravenous administration of the drugs.

In 2004 an oral 5-FU analog, capecitabine, was introduced and found to be at least equivalent to the standard 5-FU/FA regimen with a high level of stabilization and favourable toxicity profile in the metastatic setting. More recently, capecitabine has been approved as treatment for CRC in the adjuvant setting, initially in patients refractory to the 5-FU/FA regimen, subsequently as first-line treatment. It is also used in breast cancer, both as a single agent or combination with other cytostatics. It is used as replacement of 5-FU/FA in combination with oxaliplatin.

SIDE-EFFECTS

The oral drug is not without its side-effects, the most notorious being the “hand-foot syndrome” (HFS), a manifestation not unique to capecitabine – it has been known to occur with 5-FU and lyophilized doxorubicin, though more severe and debilitating.

A study by Heo found HFS in 116 out of 179 (64.8%) and in 384 04881 (43.6%) chemotherapy cycles. Grade 3 HFS was found in only 4.5% patients and 9 cycles (1.0%). The aforementioned figures might not seem to be clinically severe but sufficient to cause patient dropout.

CLINICAL MANIFESTATION AND ETIOLOGY

The clinical manifestations of HFS are characteristic, starting with dysesthesia and paresthesia of the palms of the hands and soles of the feet, including numbness and tingling. After 3 to 4 days, the initial lesions progressively develop into painful erythema and swelling, particularly on the pads of the fingers, sometimes severely disrupting the patient’s ability to carry on daily activities. If the condition progresses further, the indurated erythematous plaques darken which over the next few days became blisters followed by desquamation. Upon cessation of the drug, reepitheliation ensues and with healing. In some cases, a mild generalized edema or morbilliform rash coincides with the acral reaction.

Assessment of the condition is based on a set of criteria, most commonly used being the WHO grading system as shown in table 1.

Another more simple grading system is used by the United States National Cancer Institute (NCI), in which only 3 grades are used and related to function (Table 2).
The Use of Capecitabine in Cancer

Reducing the dose without interruption at the first signs of HFS is likely to result in worsening of the condition. With discontinuation of the drug, recovery is achieved within several weeks or even days in some patients. Following discontinuation, the standard protocol (see table 3) applies to dose reduction.

As for the use of drugs, pyridoxine (vitamin B6) has been and is still being used in HFS, as it has been known to delay and alleviate the severity of the syndrome. A newer finding is that HFS is now considered an inflammatory response mediated by the overexpression of cyclooxygenase (COX-2), and several studies have reported the benefit of the use of COX-2 inhibitors in the treatment of HFS. A very recent, though still to be tested in a larger population, is the use of urea-containing ointments. Applied locally twice a day, a urea-containing moisturizing ointment was used prophylactically and resulted in the reduction of desquamation, pain, increasing the comfort level in all patients studied in 7 cycles of capecitabine. All patients were able to complete the chemotherapy cycle as per the schedule and without interruption or delays.

In the author’s experience, and substantiated by several other authors in the literature, patient education plays an important – if not the most important – role in the management of HFS. Motivation, combined with a good system of communication between doctor and patient has consistently proven to be invaluable in the management of this potentially non-life threatening but potentially very debilitating condition.

<table>
<thead>
<tr>
<th>WHO grade</th>
<th>WHO definition</th>
<th>Clinical lesion</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dysesthesia/paresthesia tingling in hands and feet</td>
<td>Erythema</td>
<td>Dilated blood vessels of the superficial dermal plexus</td>
</tr>
<tr>
<td></td>
<td>Discomfort in holding objects and upon walking, painless swelling/erythema</td>
<td>1+edema</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Painful erythema/swelling of palms and soles, periungual erythema and swelling</td>
<td>2+fissuration</td>
<td>Isolated necrotic keratocytes in high layer of epidemis</td>
</tr>
<tr>
<td>3</td>
<td>Desquamation, ulceration</td>
<td>3+blister</td>
<td>Complete epidermal necrosis</td>
</tr>
</tbody>
</table>

Table 1. World Health Organization (WHO) Grading for HFS in Capecitabine Therapy

<table>
<thead>
<tr>
<th>NCI grade</th>
<th>NCI definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Skin changes or dermatitis without pain, e.g. erythema, peeling</td>
</tr>
<tr>
<td>2</td>
<td>Skin changes with pain, not interfering with function</td>
</tr>
<tr>
<td>3</td>
<td>Skin changes with pain interfering with function</td>
</tr>
</tbody>
</table>

Table 2. National Cancer Institute (NCI) Grading for HFS

The mechanism of HFS remains unclear – the known fact is that it is dose dependent and probably related to drug accumulation in the skin. Hands and feet, like tumor cells, may potentially accumulate more 5-FU. There are at present two theories based on different underlying pathology. The first involves specialized skin cells (keratinocytes) which upgrade the levels of the enzyme thymidine phosphorylase thus resulting in a “toxic cellular state”; the second theory refers to the finding that capecitabine may be eliminated by the eccrine system (sweat secretion), resulting in HFS caused by an unknown mechanism relating to the increased number of eccrine glands on the hands and feet.

Recent studies have reported that HFS is caused by capecitabine’s metabolites, and probably prostaglandin-like in action. It is also reported to be driven by COX-2 as a central regulatory mediator of inflammation. This phenomenon is presently being studied in the therapeutic approach to HFS.

TREATMENT

There are two lines of approach to the problem, i.e.: 1) Dose modification, and 2) Drug intervention. The modification of dose subsequently followed by dose reduction should be the mainstay of HFS management. Reducing the dose without interruption at the first signs of HFS is likely to result in worsening of the condition. With discontinuation of the drug, recovery is achieved within several weeks or even days in some patients. Following discontinuation, the standard protocol (see table 3) applies to dose reduction.

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REFERENCES


Table 3. Capecitabine Dose-modification Scheme for All Adverse Events

<table>
<thead>
<tr>
<th>NCI-CTC toxicity grade</th>
<th>Appearance of toxicity</th>
<th>Adjustment during therapy</th>
<th>Adjustment for next cycle (relative to initial dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st</td>
<td></td>
<td>Interrupt until resolved to grade 0/1</td>
<td>100%</td>
</tr>
<tr>
<td>2nd</td>
<td></td>
<td>Interrupt until resolved to grade 0/1</td>
<td>75%</td>
</tr>
<tr>
<td>3rd</td>
<td></td>
<td>Interrupt until resolved to grade 0/1</td>
<td>50%</td>
</tr>
<tr>
<td>4th</td>
<td></td>
<td>Discontinue drug permanently</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1st</td>
<td>Interrupt until resolved to grade 0/1</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>2nd</td>
<td>Interrupt until resolved to grade 0/1</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>3rd</td>
<td>Discontinue drug permanently</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4th</td>
<td>Discontinue drug permanently or interrupt until resolved to grade 0/1</td>
<td>50%</td>
</tr>
</tbody>
</table>

NCI-CTC, National Cancer Institute Common Toxicity Criteria.

a Not applicable to HFS.

b At discretion of the clinician.