Patient Selection for Oral Chemotherapy

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Oral chemotherapy has evolved with several new agents such as capecitabine, UFT, eniluracil, etc. in active clinical trials or already approved for use in the western world. Several distinct issues, apart from the usual criteria

Introduction

Oral agents such as busulfan (Busulfex, Myleran) and hydroxyurea (Hydrea) have been available for clinical use for the last 3 decades. Several newer agents such as capecitabine (Xeloda), eniluracil, and UFT (Orzel) are currently being used or investigated all over the world, and the clinical uses of these agents are likely to expand over the next few decades. This article discusses the various issues that need to be considered in selecting patients for administration of these agents.

Oral Chemotherapy: Challenges

The development of oral agents for clinical use presents several challenges. Absorption of oral agents is a complex process and can involve passive diffusion or active transport in the gastrointestinal tract. In patients with several types of cancer, patients often develop an underlying gastrointestinal motility disorder. These disorders may be related to (1) surgical procedures such as colon, small bowel, and gastric resections[1-10], (2) the result of hormonal secretions from tumors, or (3) the complications of chemotherapy itself, (ie, diarrhea and nausea). In addition, patients with swallowing problems, compliance problems, geriatric patients, and other special groups of patients may have difficulty in understanding or following the instructions for self-administration of these oral regimens.

Patient Preference

In a study conducted by Liu et al[11], the preference of 103 patients with incurable cancer for intravenous vs oral chemotherapy was assessed via questionnaire. The survey showed that 92 patients (89%) preferred oral chemotherapy; however, a majority (70%-74%) were not willing to accept a shorter duration or lesser response with oral therapy. Most patients (71%) wanted active physician participation in guiding their decision to take oral vs intravenous therapy and most patients attributed their preference for oral chemotherapy to convenience and problems with intravenous access. Although this was a small study, it provided some insight into the patient preference issue and added to physician awareness of the issues surrounding oral chemotherapy development.

Patient Compliance

The effect of dose intensity is well documented in several solid tumors in the adjuvant setting, eg breast, colon, and ovarian cancer.[12,13] It is especially important in the treatment of Hodgkin’s disease and other hematologic malignancies.[14] In the seminal study by Bonadonna,[12] women with breast cancer who missed more than 15% of doses had a worse outcome compared to women who received full doses of chemotherapy.

Various factors affect compliance of patients with oral chemotherapy and compliance can have a profound effect on the delivered dose intensity of an oral agent. These factors include socioeconomic status, educational level, patient-physician communication, complexity of treatment regimen, and unrecognized depression in patients.
Why Compliance Varies

In one study of 51 patients with breast cancer, compliance to treatment with oral cyclophosphamide (Cytoxan) was measured prospectively, with pill counting and other questionnaire methods.[15] Noncompliance with treatment was defined as an intake of < 90% or > 110% of the normal dose of cyclophosphamide. Patients in the academic practice setting achieved higher (67%) overall compliance than did patients in the private practice setting (20%).

In another study,[16] plasma levels of prednisone and allopurinol (Zyloprim) were used to monitor the compliance with oral therapy of patients with multiple myeloma. In this study, the compliance rates were quite low (16% to 24%) but increased substantially (44%) after appropriate patient education. The authors found self-reporting to be inaccurate in this trial.

Lee et al tested compliance with oral therapy in patients with lymphoma, ovarian cancer, and lung cancer in three different trials.[17-19] In these trials, in addition to self reporting, an "intelligent" bottle electronically monitored patient compliance. The authors found compliance to be in excess of 90% with good concordance of self reporting and electronic monitoring. It was not clear, however, if the patients who participated in the study were aware of the alternative monitoring method.

In a large, recent randomized phase II trial of capecitabine in colon cancer patients,[20] no major compliance problems were reported although this subject was not explicitly addressed.

In summary, patient compliance is a complicated issue and can depend on the population studied, methods utilized to study compliance, and patient education.

Concomitant Medications

It is always relevant to obtain a detailed medication history for the patient prior to prescribing oral chemotherapy. This is important for retaining the bioavailability of oral medications. For instance, in the capecitabine trial, patients were instructed to take capecitabine with water at 12 hour intervals within 30 minutes after ingestion of food. In addition, patients were instructed to avoid simultaneous intake of antacids. Patient education, thus, becomes vitally important. In spite of precautions, severe drug interactions are possible.

In a Japanese trial of tegafur, 18 deaths were attributed to simultaneous intake of the antiviral drug, sorivudine.[21] A metabolite of sorivudine was thought to have inhibited dihydropyrimidine dehydrogenase, the enzyme required for metabolism of the fluoropyrimidines.

Patient Selection

Although oral chemotherapy has been widely perceived to be patient friendly, several issues need careful consideration before these medications can be prescribed. The most important assessment that needs to be made concerns patient reliability. Generally speaking, these medications should be avoided in patients who are not likely to be able to reliably take most doses of the oral drugs prescribed for them. Such patient populations include those with significant oropharyngeal disability, significant gastrointestinal problems, eg fistulae, bowel obstruction etc, and geriatric patients with dementia, depression, etc. Efforts should also be made to avoid prescribing oral drugs to patients who have demonstrated unreliable behavior or lack of motivation in the past, including missing doctor visits for unexplained reasons. Patients who have a known history of self modulating doses of other medications in the past may also be poor candidates for oral chemotherapy.

In addition, the prescribing oncologist must ensure that compliance is monitored by various techniques, such as interviews, pill counting, telephone follow-ups, etc. The use of novel methods like intelligent bottles for assessing compliance requires further validation in clinical trials.

The Education Factor
One other major factor for assuring safe and effective oral chemotherapy is patient education. Oncology staff in the outpatient setting need to make use of all possible opportunities to educate patients about chemotherapy intake at home. In addition, they must be available to answer questions and encourage patients to call before self-modulating doses of therapy and taking concomitant medications.

The era of oral chemotherapy has arrived. Several newer drugs are likely to be approved for use soon. In addition to the opportunity for patient-friendly and effective therapy, these drugs also generate novel challenges for the practicing oncologist. Further clinical experience at clinical trials will help define the optimal patients for treatment with oral chemotherapy.

**References:**
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