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Oral Cancer Chemotherapy: The Critical Interplay Between Patient Education and Patient Safety

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Abstract

Currently, 10% of cancer chemotherapy is prescribed to patients by means of an oral formulation, but, by 2013, this percentage is predicted to increase to 25%. Oral chemotherapy offers many advantages, including no need for sometimes painful intravenous access, no intravenous drug administration fees, more time at home for patients, and a greater sense of patient autonomy. However, oral cancer chemotherapy also poses challenges, many of which revolve around adherence and safety. These challenges are discussed here. There are few other circumstances in which patient education and the maintenance of institutional safety infrastructure play such an integral role in sustaining favorable cancer clinical outcomes.

Keywords

Oral chemotherapy; Education; Side effects; Capecitabine; Temozolomide; Safety

Introduction

"Sisyphus was promoted at work. He got a bigger stone" [1]. This analogy is apt for oral cancer chemotherapy, which provides a similar type of dual—seemingly favorable but also unfavorable—set of circumstances for cancer patients, their families, and health care providers. Such circumstances are particularly relevant in the setting of a rapidly expanding utilization of this method of drug administration. Currently, 10% of cancer chemotherapy is provided to patients as an oral formulation, but the National Comprehensive Cancer Network predicts that by the year 2013 this percentage will jump to 25% [2].

Between the years 2005 and 2007, over a dozen new oral cancer chemotherapy agents had been approved by the US Food and Drug Administration, a trend that perhaps suggests many more such oral cancer agents will enter into clinical practice in the near future [3]. New agents in development are heterogenous. Although some are cytotoxic, it is anticipated that the majority of oral drugs to be approved in the future will have more targeted antineoplastic

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effects. Nonetheless, these agents are expected to carry side effects and, to some extent, a narrow therapeutic dose range. The topic of oral cancer chemotherapy, its advantages and disadvantages, and how best to maximize its safety is timely.

At first glance, oral chemotherapy appears to provide only benefits. With oral chemotherapy, the cumbersome and painful aspects of acquiring intravenous access vanish; administration fees associated with intravenous access are eradicated; patients spend more time in their own homes, as opposed to in a clinic where they might otherwise be receiving a drug infusion over several hours; and cancer patients are also put in a position of greater autonomy in which they are the ones who have greater control over their cancer treatment because they are the ones administering the drug [4, 5]. There is no question that oral cancer chemotherapy offers advantages, which, in effect, “promote” the well-being of cancer patients and their families.

Yet, in addition to these generally positive effects, oral chemotherapy carries with it other concerns. This review discusses these concerns, and it also discusses some of the “heavy lifting”—patient education efforts as well as the development and maintenance of institutional safety infrastructure—that health care providers must perpetually utilize when prescribing oral cancer agents.

Oral Chemotherapy Misconceptions

Surprisingly, oral chemotherapy brings with it misconceptions about side effects and efficacy. In talking with patients, our clinical experience suggests that many patients and their family members believe that oral chemotherapy has minimal, if any, side effects. In reality, although some oral agents may be reasonably well tolerated, all have side effects. Comparative studies between oral agents and intravenous agents, both of which have similar mechanisms of action, suggest that side effect profiles may be somewhat more favorable with oral chemotherapy. There is no doubt, however, that side effect profiles are not negligible. For example, Twelves and others [6] conducted a phase 3 trial that compared adjuvant capecitabine (an oral medication) to 5-fluorouracil (an intravenous drug given as part of the Mayo regimen) in postoperative colon cancer patients. Studying a total of 1,987 randomly assigned patients, these investigators observed that the disease-free survival was at least equivalent with oral chemotherapy and that significantly fewer side effects occurred with capecitabine. However, if one probes further, one sees that certain side effects were in fact more severe with oral therapy. Specifically, the rate of hand-foot syndrome was 60% with capecitabine in contrast to 9% with the intravenous chemotherapy. Hyperbilirubinemia occurred in 50% of patients with capecitabine but in only 20% of intravenously treated patients. The overall side effect profile might have been more favorable with oral chemotherapy, but it was by no means benign and in fact some side effects occurred more frequently with the use of the oral agent.

Furthermore, some newer oral chemotherapy agents may cause unusual side effects or those that are not easily recognized. Such side effects include skin rash or more subtle events such as hypertension and thyroid dysfunction. A prompt recognition of such side effects can lead to better control of treatment-related symptoms [7].

Another perilous issue entails drug interactions. The risk of drug interactions is also not negligible in a setting where patients are on an extended course of continuous drug therapy. Patients can start another medication that might interfere with the absorption or bioavailability of their oral chemotherapy agent or vice versa. Warfarin is a frequent culprit. Shah and others [8] performed a retrospective study of 77 patients who were prescribed capecitabine. Twenty-one of these patients had received warfarin along with the capecitabine. Six of these patients required a warfarin dose reduction presumably because of supra-therapeutic coagulation parameters, and there were a total of five episodes of gastrointestinal bleeding with warfarin. In short, 5 of 21 patients, or 24%, experienced clinical morbidity from this drug interaction. This degree of morbidity emphasizes once again the importance of educating patients on the point that oral chemotherapy is not benign, that the initiation of new drugs should be preceded by in-depth conversations with all members of the health care team, including the patient, and that sometimes greater vigilance in monitoring is in order.

Yet another misconception on the part of cancer patients is that oral chemotherapy is less effective than intravenous therapy. In a survey of 59 patients starting oral chemotherapy for metastatic breast cancer, Catania and others [9] observed that approximately 10% of patients thought that oral chemotherapy was a last-ditch effort. In effect, although these patients were willing to accept oral treatment, they perceived the treatment as suboptimal and appear not to have been totally understanding of the goals of cancer therapy.

With regard to the latter, a growing body of literature works to dispel this misperception that oral chemotherapy is always inferior in efficacy to intravenous chemotherapy [10, 11], and three examples are cited here. First, as alluded to earlier, adjuvant capecitabine in colon cancer patients seems comparable in efficacy to intravenous 5-fluorouracil, as administered as the Mayo regimen [6]. Second, emerging studies suggest that even oral agents that work by means of very different mechanisms might yield favorable clinical outcomes, as illustrated in a study from Mok and others [12•]. These investigators reported on treatment-naïve, metastatic non–small cell lung cancer patients from East Asia. All these patients had adenocarcinoma and were nonsmokers or former light smokers. This cohort of 1,217 patients was randomly assigned to receive either gefitinib, an oral epidermal growth factor receptor inhibitor, versus a combination of carboplatin and paclitaxel. The 12-month rate of progression-free survival with gefitinib was 25%, and with the conventional intravenous chemotherapy it was 7%. Third, oral therapy for chronic myeloid leukemia is highly effective, more so than many previously used forms of intravenous chemotherapy. Imatinib provides a breakthrough for patients with a fatal disease [13]. These observations indicate that oral cancer treatment should not necessarily be perceived by cancer patients or their families as inferior to intravenous treatment.

Taken together, the foregoing provides a clear message to health care providers: it is imperative that patient education be incorporated into prescribing practices and that the fact be emphasized that oral cancer therapy must be taken seriously. These oral agents clearly have side effects, some of which exceed the prevalence and severity of those observed with intravenous chemotherapy. Again, patients must be told this. Patients must also be frankly apprised of the potential benefits of oral therapy in the same manner as they would of

intravenous chemotherapy. Certainly, not all oral chemotherapy under all circumstances will yield benefit just as not all intravenous chemotherapy will yield benefit. Patients should not, however, leave an oncologist's office thinking that oral therapy represents a last-ditch effort for the sole and sheer reason that they have walked away with an oral prescription in hand. Understanding some of these potential misperceptions on the part of the patient and addressing them in a preemptive fashion might help promote better adherence to oral chemotherapy regimens, as further discussed below.

The Problem of Adherence

Is adherence really a problem with oral cancer treatment? The published literature suggests it is. In the case of intravenous chemotherapy, the patient is in the clinic, and the treatment is witnessed—indeed administered—directly by a health care provider. In contrast, adherence, in general, tends to be relatively poor with oral chemotherapy. Decker and others [14] observed that as many as 23% of patients did not take their oral chemotherapy in the manner in which it had been prescribed either because of symptoms that arose or because they had merely forgotten to take the medication. Providing corroborating statistics, Grunfeld et al. [15] described a 12% rate of nonadherence with tamoxifen, and Ziller et al. [16] described a 20% to 30% rate of nonadherence again with adjuvant hormonal therapy for breast cancer.

Although as presented above, these rates are not negligible, they may even be erroneously low. The very fact that patients are being monitored and assessed is likely to boost adherence (the so-called Hawthorne effect) or to boost the appearance of adherence. The prospect of returning wasted pills to an oncologist's office and having each one be counted could potentially result in patients discarding such pills prior to their doctor's appointment to avoid a sense of embarrassment and to increase the appearance of having been adherent to medication instructions. Similarly, investigators have utilized other approaches to assess drug adherence such as the use of a micro-electronic monitoring system that provides a charged pill bottle cap that electronically monitors and records every time the pill bottle is opened. Such methods are of value, but, again, if a patient knows that he or she is being monitored for adherence—as is typically the requirement of every Institutional Review Board–approved clinical study on medication adherence—there is a possibility that that patient might manipulate the cap to indicate an inaccurately higher level of medication adherence.

Is adherence truly important, and, if so, why are patients not more adherent? A study from McCowan and others [17•] demonstrates that this issue is not trivial. This study examined the effect of medication adherence with tamoxifen on mortality. Records of purchased prescriptions were used to assess adherence. Ninety-three percent of patients were adherent, but those patients with an adherence rate of <80% manifested a poorer survival: hazard ratio = 1.10, 95% confidence interval = 1.001–1.21. This statistic, which starkly illustrates how medication adherence can be associated with life and death outcomes, underscores the importance of ensuring adherence.

Moreover, lest any aspect of this review suggest that poor adherence represents nothing more than a patient's forgetting to take a medicine on occasion, a further discussion of the

complexity of poor adherence is in order. Certainly, forgetting to take a daily medication can be a major issue, and various devices, such as daily calendar-formatted pill boxes, can be of value in helping patients remember. However, issues that revolve around adherence are even more complicated. Patients may stop taking an oral agent because of fears of side effects, disbelief in the efficacy of the treatment (as alluded to earlier), financial limitations that preclude their ability to acquire the medication, misunderstood directions on how to take the medication, or, at times, a total lack of any direction on how to take the medication. Poor adherence is complicated, yet it does at times carry grave consequences.

It should be noted that adherence pertains not only to taking an oral chemotherapy agent, but also to not taking the agent. A desire to keep taking a drug regardless of consequences, even when notable side effects are occurring, can also be detrimental. Under these circumstances too, instructing patients to hold therapy in the event of extreme side effects is an important aspect of prescribing oral agents. In fact, within our institutions, patients are told to stop such agents as capecitabine first and then call the health care provider—in this sequence—in the event of diarrhea, mucositis, severe hand and foot syndrome, or other challenging side effects. A delay in reaching the health care provider can conceivably lead to continued drug therapy that in turn would lead to a progressive increase in debilitating, potentially dangerous side effects. In short, adherence refers not only to deliberatively taking the oral drug as initially instructed but also to deliberatively stopping it when appropriate.

To summarize further, a recent *Cochrane Review* on patient counseling suggests better patient outcomes when a pharmacist provides patient education on pill-taking [18]. This meta-analysis included 2,246 patients from 13 studies and focused on hypertension. Pharmacists' interventions significantly reduced systolic blood pressure (10.7±11.6 mm Hg; P=0.002), whereas in control groups, it did not (3.2±12.1 mm Hg; *P*=0.361). Admittedly, this *Cochrane Review* did not focus on oral cancer drugs, but nonetheless the point of this publication is well taken. Providing patients with a good educational background on when and how to take their medications is of paramount importance. A patient-oriented conversation that elicits and addresses concerns about side effects and efficacy of therapy is of value. Talking about the cost of the oral medication up front and learning about financial impediments to drug acquisition allows for the earlier consideration of alternative treatment strategies. Even instructing patients on adherence tools such as calendar pill boxes helps patients take oral medications more effectively.

Food Effect: Educating Patients on the Mundane

Of relevance, a growing literature demonstrates the importance of instructing patients on the mundane variable of food intake. Drug absorption rates vary based on the latter, an observation that makes the point that patients should be counseled on this issue as well. Changes in how one takes medication based on food intake can contribute tremendous variability to absorption and stable levels of certain drugs, even cancer drugs. Reigner and others [19] demonstrated that fasting increases the rate of absorption of capecitabine. If food is ingested 30 min prior to capecitabine, the absorption of this drug appears to be relatively stable. However, if patients are fasting before this drug, there can be great variability in drug absorption, thereby leading to erratic side effects. Thus, patients should always be instructed

to take capecitabine with water within 30 min of eating, and, in general, education on food intake with medication usage should be provided to all patients regardless of what type of oral cancer agent is prescribed.

An extreme example of this food effect is seen with lapatinib. Koch and others [20•] looked at plasma concentrations of lapatinib based on whether a high-fat breakfast versus a low-fat breakfast had preceded the taking of this oral drug. Notable differences arose in how lapatinib was absorbed within these groups based on earlier dietary intake. A high-fat breakfast led to a major increase in absorption of lapatinib, as great as a 4.25-fold increase, in area under the curve compared to what was seen in a fasting state. A low-fat breakfast led to a 2.67-fold increase in the area under the curve. Again, food intake and even type of food intake may have marked consequences relevant to drug efficacy and subsequent side effects. Consistent patient instructions on how to take an oral drug have a marked impact on how patients will tolerate a drug and perhaps also on the derived benefits.

Yet Another Mundane Factor Relevant to Adherence: Scheduling Pills

What else can health care providers do to help patients with adherence? One major, but in our opinion under-studied, approach deals with the frequency of pill administration. Buzdar and others [21] demonstrated that 20 mg of tamoxifen taken once daily is bi-equivalent to 10 mg of tamoxifen taken twice daily. Although these days this type of observation may not receive the same kudos as those yielded by other more cutting-edge research efforts, there is nonetheless pragmatic value in this finding. This research consolidates the dosing of a drug, may improve compliance, and appears to make it easier for patients to remember to take their medications on a daily basis. From a health care provider's standpoint, such consolidated dosing should influence prescribing practices, thereby allowing health care providers to make it easier for patients.

The Real Heavy Lifting

Perhaps the toil of Sisyphus is best illustrated by the need to maintain perpetually vigilant institutional safety infrastructure to enable oral chemotherapy to be consistently prescribed in a safe fashion. This is where much of the behind-the-scenes "heavy lifting" with oral chemotherapy really occurs.

The American Society of Clinical Oncology/Oncology Nursing Society recently drafted guidelines for the administration of all chemotherapy [22•]. These guidelines discuss how the administration of chemotherapy should be preceded by at least one independent dose check after leaving the hands of the health care provider. With some oral chemotherapy agents, such as capecitabine and temozolomide, a patient's height and weight are necessary to calculate dosing, and yet retail pharmacists with no specialty training in cancer drugs may not be facile in performing such calculations and may not even have the necessary clinical information to conduct such a double-check. Thus, prescription errors can occur unnoticed. Although intravenous chemotherapy is commonly double-checked by nursing staff and pharmacy staff at many cancer centers, these double-checks are stripped away with

oral chemotherapy. Parallel infrastructure for double-checking oral chemotherapy is lacking at many institutions [23].

At the Mayo Clinic, a series of steps were recently put in place to enable an independent double-check of some oral chemotherapy agents by pharmacy staff with expertise in oral cancer chemotherapy. This double-check occurs regardless of whether patients will be having their oral chemotherapy prescription filled at the Mayo Clinic or at an external pharmacy. The Mayo infrastructure for the double-check focuses specifically on capecitabine and temozolomide, both of which require a dose calculation.

The benefits of this double-check are manifold. First and foremost, it helps ensure that patients receive the intended dose of drug. Second, merely implementing a double-check of oral chemotherapy appears to lead to a drop in erroneous prescription writing. For example, initially the “near miss” rate in prescribing oral chemotherapy, defined as a 10% or greater difference between the written and intended dose of oral chemotherapy drug, was 3.7% after approximately 1 month of monitoring and double-checking (data submitted). However, after a few more months, this rate progressively dropped to a low of 0.8%. The fact that providers were called about erroneous prescriptions appears to have prompted them to improve the accuracy of their prescriptions. Third, this double-check calls attention to particularly problematic oral chemotherapy agents. In looking at these “near misses,” capecitabine, not temozolomide, resulted in a greater number of erroneous prescriptions, despite the fact that there were more prescriptions written for the latter (data submitted). Capecitabine is a drug with multiple different dosing schedules: some providers prescribe it for 3 weeks straight; others for 2 weeks straight; others ask patients to stop the drug on weekends during radiation treatments. This panoply of regimens can lead to a variety of dosing errors or misunderstandings on the part of patients. Capecitabine also comes in various tablets of different strength, and it often calls for twice-a-day dosing—two other variables that further complicate how it is prescribed and potentially spawn errors. Thus, there appears to be a role for developing safety infrastructure and educational materials that are highly specific to capecitabine. Although new oral chemotherapy agents are rapidly emerging and although a thorough approach to safety is best, if it is feasible for an institution to double-check one and only one commonly prescribed oral chemotherapy agent, perhaps for now it should be capecitabine.

Conclusions

Oral cancer chemotherapy has the potential to benefit patients, but we believe that its administration also invokes safety issues that require continued acknowledgment. These agents can definitely provide clinical benefit to patients, but they are perhaps best prescribed in conjunction with major educational efforts and in a setting where other solid safety infrastructure is also in place. As more oral agents become available, the importance of such efforts and infrastructure will only grow.

Acknowledgment

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