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Care of the Elderly Patient on Oral Oncolytics for Advanced Disease

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Abstract

Oral oncolytics are now a common component of cancer care for older individuals with advanced cancer when a new treatment regimen is needed. Many of the solid tumors in elderly patients may respond to the oral oncolytics, however not without side effects and challenges to maintain adherence. This article describes some of the important areas to be considered when oral oncolytics are prescribed for elderly patients. A general overview of important intervention areas of focus is included.

Keywords

Geriatrics; oral oncolytics; cancer patient; medications

Introduction

The highest incidence of most solid tumor cancers occurs among older adults where the median age is around 65. While the median age at diagnosis for breast cancer is 61, 43% of all breast cancers occur in patients 65 years of age and older. For other solid tumor cancers the median age at diagnosis are: 71 for pancreatic, 66 for prostate, 70 for lung, 64 for kidney, 70 for colon and 68 for colorectal cancer [1]. Over the course of their disease many of these older patients receive multiple lines of treatment extending from curative to palliative intent. Oral oncolytic agents are frequently prescribed to extend the time to disease progression once earlier lines of treatment have failed. At this time there is at least one FDA approved targeted agent for each of the cancer sites listed above. More than 30% of the antineoplastic agents in the US Food and Drugs Administration pipeline are oral agents [2].

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Compliance with Ethics Guidelines

Conflict of Interest

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Human and Animal Rights and Informed Consent

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Use of Oral Targeted Agents

Unlike general cytotoxic drugs that act on all normal and rapidly dividing malignant cells, oral targeted agents focus on molecular targets and are designed to block key regulators of a cancer cell's growth and development. Oral oncolytic agents bind to a specific protein or nucleic acid in order to alter the activity or function of the target. Oral oncolytics are targeted therapies known as molecular targeted therapy or biological therapy that blocks the growth and progression of malignant cells by interfering with distant pathways needed for development and growth of tumors [3].

Common classifications include Tyrosine Kinase inhibitors (VEGFR and EGFR) (ex. sorafenib, regorafenib, sunitinib) and Cytotoxic agents. While these agents are targeted they, nevertheless, may interact with other medications prescribed to manage chronic comorbid conditions. For example, Kinase inhibitors interact with a variety of drugs such as H2 blockers, or proton pump inhibitors with CYP3A inhibitors such as dexamethasone, phenobarbital, St. John's Wort. Others include warfarin, antihypertensive, corticosteroids, and anticonvulsants. Consumption of grapefruit and Seville oranges for example can result in alteration of the bioavailability of the Kinase inhibitors. There are a variety of classifications of drugs, the major categories are listed in Table 1.

Because of their molecular action and oral administration, targeted agents have been welcomed by patients and oncologists [4]. However, oral cancer oncolytics pose challenges to older patients and their families as well as their health care professionals. For the older adult, challenges revolve around adherence and persistence in order to remain on the drug, managing numerous side effects, difficulties posed by the dosing complexity of the regimen, and the polypharmacy associated with other medications to manage ongoing comorbid conditions. Cardiovascular, gastrointestinal, dermatologic and hematologic side effects may pose problems for the elderly. Further, many patients may face substantial out-of-pocket costs associated with the high copays for these very expensive medications.

In this article we cover some of the important issues older patients with advanced cancer face when prescribed oral oncolytics. Among the common concerns for the older patient with cancer taking oral oncolytics are their potential impact on physical function, comorbidity, side effects, polypharmacy, cognition, adherence, nutrition, psychological status, and safety. Some suggestions for interventions will be offered.

Among older cancer patients, treatment with oral agents poses both positive and negative factors. Unlike the waiting, extended numbers of clinic visits, and discomfort associated with intravenous treatment, patients on oral medications receive their medications, often by mail from specialty pharmacies, and need to spend little time administering their medications, compared to intravenous chemotherapy in clinical settings. Frequently, however, in addition to oral agents patients are on intravenous therapy or even injections such as hormones as a part of their treatment regimen. Patients who only have oral agents prescribed, while freed from the frequent travel and extended visits, must assume accountability and responsibility for medication administration including dosing, which may cause problems and greater treatment burden. This is especially problematic for those who

have multiple medications for chronic diseases [5]. Because of the complexity of the cancer treatment regimens, patients may be unclear as to the extent of their role in the monitoring and management of medication side effects that emerge. For the older patient with multiple chronic diseases and advanced disease, managing multiple medications, handling the medication, and organizing administration schedules including the stipulations for food and fluids, is often an overwhelming responsibility.

Physical Function

Physical function is an important barometer of the health of older cancer patients. For older patients who have been prescribed oral oncolytic agents, an unexpected decline in physical function is an important signal for oncologists and primary care physicians. Is the oral agent having a direct effect on the neuro-muscular system and threatening cognition, balance, coordination, motor skills or gait? Oral agents may have indirect effects through interactions with other medications to produce new side effects or by neutralizing the effect of another medication, or possibly through the side effects and symptoms it produces, which in turn make functioning more difficult. A number of oral agents (ex: palbociclib, sorafenib, thalidomide) increase the risk of older patients experiencing peripheral neuropathy which can cause disability due to pain, parathesia, weakness, numbness, tingling, gait, unsteadiness, balance, and potential falls. The frequency of occurrence and severity of peripheral neuropathy with diminished sensation are increased with some oral oncolytics (such as crizotinib or thalidomide) and accentuated for some patients, such as those with diabetes. Another condition that may occur is hand foot syndrome which results in edema of hands and feet, blisters and pain limiting self-care and physical function (ex. afatinib, axitinib, capecitabine, pazopanib, sorafenib, sunitinib).

Other side effects from advanced disease and oral agent treatment that affect physical function include anemia, overall weakness, arthralgia, extremity edema, and fatigue [6]. Some patients may enter their cancer treatment with some functional disability due to previous fractures, arthritis, and overall deconditioning and the frailty of aging. In sum, it is not chronological age that must be considered when initiating cancer treatment with oral oncolytics. But, instead, the physical health of the patient that is a consequence of the side effects produced by the oral agents alone, or in interactions with their other medications to manage ongoing chronic conditions that must be balanced with the oral oncolytic during treatment. The potential for these treatments to accelerate frailty requires not only careful assessment prior to initiating treatment, but careful monitoring during treatment and engagement of the patient to report significant changes and side effects. Patients must be informed and monitored to assure that they implement self-care strategies to prevent or reduce the impact of these side effects. Changing physical function should be assessed. At times physical therapy may be of benefit.

Comorbidity- Multimorbidity

Evaluation of patients' comorbid conditions is critical to the decisions to prescribe oral agents and to continue to monitor the patient's response to the treatment. Certain comorbid conditions, in the presence of some oral agents, will increase the likelihood of side effects

and drug to drug interactions. Patients with underlying diabetic neuropathy are at increased risk for accelerated and severe peripheral neuropathy when prescribed drugs such as crizotinib. Cardiac history may be aggravated by certain oral agents as well. Myocardial infarction (MI), congestive heart failure (CHF), and atrial fibrillation may be exacerbated by oral agents (ex: dabrafenib, dasatinib, erlotinib and lenalidomide), while other drugs evoke hypertension and necessitate careful monitoring (ex: abiraterone acetate, axitinib, enzalutamide).

Older patients often present with several other chronic diseases (hypertension, cardiopulmonary, diabetes, hepatic, and renal diseases) which may be equally important to manage for the patient's quality of life and to optimize cancer treatment outcomes. All of the chronic diseases are likely to affect and be affected by the cancer and cancer treatment. Cohen and colleagues [7] documented that physical function scores decreased by five for every comorbidity. Thus certain oral cancer drugs need to be used with caution and careful monitoring for those with comorbid conditions. Hermosillo-Rodriguez and colleagues [8] found that there was increased health care resource utilization for cancer patients with common comorbid conditions.

Common Side Effects

Oral agents may be reasonably well tolerated by older patients, but they all have some side effects and are by no means benign. Many of these agents have interactions with other drugs patients may take such as anticoagulants. Drug to drug interactions should be determined. Among older persons a cascade of events may occur due to the side effects of the medications.

Cohen and colleagues [7] demonstrated that increased levels of symptoms were strongly associated with declines in physical function. Severity of symptoms and side effects may also affect other abilities of patients and extend to their psychological and cognitive function and overall quality of life. Although oral oncolytics were designed to minimize toxicities, they are not without adverse effects and complications. Common side effects include those listed in Table 2.

It is important to recognize that while these symptoms and side effects have been reported as potential side effects or adverse events in FDA drug approvals, each patient responds somewhat differently depending on pre-existing disease and medications. Oral agents, either alone or in combinations with other medications, produce diarrhea which can quickly add to dehydration, or patients with preexisting cardiac disease can quickly get into an acute cardiac event. Anemia, neutropenia and thrombocytopenia are common side effects of some oral cancer treatment in the elderly.

Certain side effects may in fact be more severe and more prevalent with oral therapy. For example, the rate of hand-foot syndrome was about 60% with capecitabine in contrast to 9% with its intravenous counterpart, 5-fluorouracil. Hyperbilirubinemia occurred in 50% of patients with capecitabine but in only 20% of intravenously treated patients [9]. Some oral chemotherapy agents may cause side effects that are not easily recognized nor easily

managed. Such side effects include skin rash, or more subtle events such as hypertension, hyperglycemia, and thyroid dysfunction. Patients are expected to know how to monitor, detect early and then manage these effects. To report these effects in timely manner, patients need to be educated and able to monitor and identify changes as they begin to appear. For the older person, written instructions should be provided, they need a non-hurried environment to review and understand the instructions.

Polypharmacy and Drug to Drug Interactions

The older cancer patients on oral agents are often on five or more medications for their other comorbid conditions at the point they initiate treatment with oral oncolytics. Polypharmacy and inappropriate medication use is common among older cancer patients. Prithviraj and colleagues [10] found polypharmacy at 80% and inappropriate medications at 41%. Polypharmacy among the elderly is exacerbated by the fact that many older patients are seen by multiple physicians in addition to the oncologist. Medication reconciliation should be conducted prior to beginning treatment with oral agents as there are numerous drug interactions likely to occur. Steroids, like dexamethasone, are used with numerous oral agent protocols thus adding additional potential problems. Patients often get a number of new supportive care drugs to manage side effects in addition to the oral agent. Supportive drugs such as antiemetics, stool softeners, pain medications, and steroids can all add to the potential problems for the older adult. Drug to drug, and drug-disease interactions can interfere with the efficacy of oral cancer treatments as well as accentuate the side effects.

Increased drug to drug interactions are more likely in the elderly due to gradual age related physiological changes that affect the pharmacokinetics and pharmacodynamics of the multiple medications they take. Alterations in dosage may occur due to body composition and organ function (e.g. renal drug clearance). For example, capecitabine should be used in reduced doses among patients with hepatic or renal failure and those on oral anticoagulants.

Gastrointestinal perforation, colitis, wound healing, impaired ocular toxicities such as blurred vision may occur and add to the difficulty the older cancer patient has due to cataracts, glaucoma and / or macular degeneration. Given the difficulties with medication management among older patients and the large number of medications, careful drug to drug evaluations are essential when prescribing oral agents. In addition to education about name and common side effects, it is important that they know dosage, frequency, how they take them, and they need to understand strategies for storage and handling [10].

Cognition

Many elderly screen positive for cognitive disorders and others have cognitive changes as a consequence of treatment with oral agents or due to interactions among drugs or other diseases. In addition they may have cognitive changes due to diseases such as dementia or Parkinson's disease. Toxicity and side effects from medications such as pain medications, or side effects such as fatigue can influence patients' cognitive function [11,12].

For the elderly the complex therapeutic regimens may challenge the cognitive processes which may make them less able to remember when they have taken the medication or, when and what side effects to report. Depending upon the status of the patient prior to beginning

treatment and the combinations of diseases and medications, patients may have trouble focusing and difficulty remembering such facts as names and numbers and they may have problems understanding what they are to do. Compromised cognitive function such as executive function, working memory and mental flexibility can influence treatment tolerance symptoms, adherence, and monitoring and recognizing toxicity [12]. Cognitive impairment can affect retention of information and the capacity to make decisions. As such assessing cognitive dysfunction may influence the choice of therapy for the patient [13].

The NCCN guidelines offer an algorithm on assessing the decision making capacity of patients to decide on the appropriate treatment.

Adherence

In a systematic review it was reported that rates of adherence to cancer treatment varied from 52-100% among older adults [14]. Puts and colleagues found that patient-related, therapy-related, condition-related, symptom-related, and social economic factors were all implicated in adherence rates among older patients [14]. There is little literature on adherence with the older adult and oral agents, but given the treatment regimens and complexity, unintended non adherence might occur more than intended adherence. Assessment of the capacity of the patient to understand the regimen and making it as simple as possible is important. There are numerous reminder apps for smart phones, alarms, and pill bottle caps available that might be assistive. Removing the medications from the package provided needs to be done only if the instructions indicate that it proper to do.

The impact of either cognitive factors and / or comorbidity on adherence in the elderly cancer patients have not been examined. Health professionals need to consider the status of the patient, the medications and the cancer and consider whether the patient can follow and adhere completely to their cancer treatment regimen. Factors to consider include: patient's cognitive and functional status, family support, affective health, financial status, health literacy and health beliefs. How do other existing chronic diseases and their treatments intrude on cancer treatment recommendations? What is the overall treatment burden [15] imposed by treatment interactions related to the multiple chronic diseases? Multimorbidity causes increased time in care coordination and communication among team members and a need for a multidisciplinary team. Primary care physicians along with oncologists are key, along with nurses, pharmacists, and social workers for the cancer care team for the elderly.

Nutrition

Nutritional assessment and monitoring are essential components for patients on oral agents. The oral agents have many recommendations about taking drugs with or without food and with or without fluids. This has to be considered when planning the regimen as these drugs have to be coordinated with the many other medications. Altered appetite and alterations in taste and smell may occur naturally in the elderly, and may be accentuated with oral agents. In addition there are numerous side effects that affect nutritional status such as nausea, vomiting, and anorexia as well as diarrhea with dehydration. Unintentional weight loss, greater than 5% over six months necessitates a nutritional screening. Body Mass Index

appears to be a prediction of mortality in older adults thus attention to weight changes is important.

Psychological Status

Older adults are likely to have mental health issues as they face serious and life threatening illness. Most of the issues are adjustments to the awareness that treatment choices are becoming limited. Depressive symptoms may occur and may be accentuated in patients with late stage disease on oral agents as they come to recognize that drugs from previous lines of treatment have not been effective, no options remain, and that they are facing the end of their life. Some of the oral agents such as Kinase inhibitors can induce or worsen symptoms of depression; it can be serious enough to interfere with their ability to cope with their illness. Anxiety occurs at certain phases as patients deal with the diagnosis, await news of disease progression and other points of uncertainty. Depression and anxiety may cause other symptoms such as sleep disturbance and fatigue which interfere with the elderly patient's ability to function. Patients should be assessed over the illness trajectory for the presence of emotional and mental health issues especially depression and anxiety. Counselors might be needed and there are a number of psychoeducational interventions that have been used with the older adult with these symptoms that should be considered.

Safety

Older adults have been shown to have poor medication knowledge which is necessary for safe oral agent administration practices. Si and colleagues [16] found that elderly patients failed to remember at least one of their medications, did not know precautions, could not read drug labels. Most did know doses and frequencies. Patients do not know how to dispose of their medications. Overall, knowledge about their medications may be limited.

Patients may not be able to identify strategies for safe medication use. Patients need to be able to identify and report the toxicities associated with their medications if they are to be considered safe [17]. Physical functioning and dangers due to weakness, fatigue and peripheral neuropathy have been discussed above. Cognitive status also may affect the adherence rate of older patients and poor memory could result in the safety problem of "overadherence" [18,19].

Interventions

It appears that the very well older person with little functional decline might tolerate oral cancer therapy well, while palliative and comfort care may be more appropriate for those who are more frail and with serious functional limitations. We have covered some of the areas that are important in the care of older persons or at least should be considered based on patient need. In this section we briefly discuss interventions.

We will briefly discuss a few areas of importance for interventions for older patients with advanced disease who are on oral agents. Detailed intervention discussion is beyond the scope of this paper. Palliative and end of life care, which may be a phase in the care of the older patient with advanced disease, is also beyond the scope of this paper.

It is important to carefully assess patient's expectations and preferences as treatment with oral agents starts. Providers need to explain the goals of care for the patient especially with advanced disease who are on their 2nd, 3rd, or 4th line of treatment. Interpreting and honestly applying the likely benefits with patients on expected outcomes is important. This enables patients to be engaged in making decisions about their treatment based on its effectiveness paired against the treatment toxicities and side effects, and the costs that the patient and family are likely to incur. These patients are at increased risk for cancer and treatment related problems brought on by their comorbidity and organ treatment.

Ongoing careful assessment and matching treatment approaches to patient's health status are key to the successful use of oral agents and their use in continuing treatment. The single most important component of care throughout treatment is an ongoing screening assessment. Careful geriatric assessments are needed; patients should undergo a good screening assessment such as the Comprehensive Geriatric Assessment (CGA). If findings are abnormal, a more comprehensive assessment should be completed [20]. The NCCN Guidelines Older Adult Oncology version 1.2016 [21] provides some clear directions and indicators as to when to perform the comprehensive assessment. The CGA can appraise the patients' health and factors that would interfere with the prognosis and help with treatment choices, enable more targeted supportive care, be prognostic in estimating life expectancy which will help with treatment decisions. Areas for the CGA are outlined in the NCCN Guidelines.

Interventions to help older cancer patients maintain function along with symptom management can help to maintain quality of life during treatment. Cancer patients treated with oral agents may become weak and have difficulty with physical functioning. Interventions that help them maintain their function, strength, remain mobile and to continue to exercise will facilitate their ongoing treatment. Strategies for symptom management interventions to moderate symptoms and side effects so that patients can continue their medications will also enable them to maintain their function. These two dimensions are important to include in a plan of care.

Multidimensional interventions that consider comorbidities, symptom distress, functional status and polypharmacy may do much to improve treatment tolerance thereby extending the time in treatment and ultimately improve cancer outcomes for older patients. Comprehensive geriatric assessments can help to adapt cancer treatment and the interventions based on patient's fitness or frailty [22,23].

A comprehensive printable list of medications that the patient is on needs to be maintained and monitored by a team for effectiveness, drug to drug interaction, and potential adverse events. Patients need to be supported and educated to understand their medications and should enable a safer situation.

Adherence is critical and patients need to understand that non-compliance to oral agents may negatively affect their prognosis. Education regarding management of the side effects and proper use of supportive care drugs is essential (antiemetics, antidiarrheals). Older patients will need specific indications for when it is appropriate to notify their health care

professionals. Guidelines to simplify their therapeutic regimen for multiple doses, dietary stipulations, potential drug interactions, and special storage and handling precautions (ex. gloves, no crushing) for their medications are needed [24].

Adherence can be facilitated using education strategies for instructions on administration. Behavioral strategies using adherence tools such as reminders, electronic monitoring, alarms, and smart phones applications may support adherence. One suggestion that might assist older cancer patients on oral agents is a referral to a pharmacist to assist with monitoring for adherence, toxicity, and drug interactions. Pharmacists also can provide assistance with financial concerns, access to specialty pharmacies and proper handling and disposal of these oral agents [25].

Conclusion

Care of the elderly patient with cancer will continue to increase. Oral oncolytics are increasingly common treatment options. There are few evidenced based interventions designed to help the elderly patient with these agents. We have covered some of the issues that we see with patients in our study. While we wait on the research to provide definitive information on interventions tailored and targeted to special needs of the elderly commonly have multiple chronic disease, there are a few points that apply. Basic care for all adult cancer patients should be standard. The NCCN Guidelines for Older Adult Oncology version 1.2016 [21] should be used along with the International Society of Geriatric Oncology's Consensus on Geriatric Assessment [26]. The critical component is to assess the patient status first by screening and then by a more detailed comprehensive geriatric assessment based on the results of the screening. This information will help with the decision making, determining needed symptom management or supportive care. Determining the patient's goals and values regarding the cancer management are critical. Older patients are interested in prognosis but more interested in morbidity, functional status, symptom burden, quality of life, and ability to be independent [27]. Determining their goals and preferences results in positive perspectives for older cancer patients.

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Table 1

Oral Agent Classifications

Cytotoxics
Kinase Inhibitors
BRC-ABL Tyrosine Kinase Inhibitor
VEGF/VEGFR Inhibitor
EGFR HER2/neu
ALK Inhibitor
BRAF Inhibitor
Phosphoinositide 3-Kinase Inhibitor
Cyclin Dependent Kinase (CDK) Inhibitor
MEK Inhibitor
Bruton's Tyrosine Kinase Inhibitor
JAK Inhibitor
Immunomodulatory (IMiDs)
mTOR Inhibitors
Poly ADP Ribose Polymerase (PARP) Inhibitor

Table 2

Frequent side effects and complications of oral oncolytics

Fatigue	Bleeding
Cytopenias	Muscle Cramps/Joint Pain/Arthralgia's
Peripheral Edema	Gastrointestinal toxicity (nausea, vomiting, diarrhea, constipation abdominal pain and heartburn)
Hand foot syndrome (pain, peeling)	Pain
Headaches	Periorbital Edema
Hyperglycemia	Peripheral Neuropathy
Hypertension	Rashes and other skin lesions
Weakness	Cardiac issues (heart failure, prolonged QT interval, left ventricular dysfunction)