To Treat or Not to Treat? Dilemmas when Deciding on Antineoplastic Treatment in Patients With Far Advanced Cancers

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Abstract

Patients with advanced cancers and their oncologists are often faced with difficult treatment decisions, especially when there are borderline situations of expected benefit or increased risk of complications. In this narrative review, we will explore the decision-making process for patients with advanced cancers and provide insights on how to approach this complex task, while didactically dividing the oncologist's assessments according to a mnemonic rule of the ABCDE of therapeutic decision-making. Part A (advanced cancer) recalls that the rule is to be used specifically for advanced cancers. Parts B (potential benefits) and C (clinical conditions and risks) represents the traditional risk vs benefit scale. In Part D, we discuss ways to identify and understand patients' desires, values, preferences, and beliefs. The prognostic estimation, from Part E, may function as an "adjust" for the antineoplastic treatment decision-making. Treatment decisions need to be conducted by skilled oncologists, in a patient-centered care, aiming to promote valuable oncology with lower rates of aggressive care.

Introduction

Clinical oncology has come a long way in recent decades, moving from a phase focused on cytotoxic antineoplastics to the era of personalized medicine, which includes numerous new molecularly targeted drugs, such as a focus on several driver mutations and signaling pathways (such as BRAF, HER2, ALK, PI3K, PTEN, FGF).[1] Other examples are the effective use of ADP ribose polymerase inhibitors (PARPi) for the treatment of ovarian and breast BRCA-mutated cancers[2] and the new antibody-drug conjugate drugs,[3] such as Trastuzumab Entamsine, Sacituzumab Govitecan, and Trastuzumab deruxtecan, for the treatment of breast cancer. In addition, the use of immune checkpoint inhibitors is revolutionizing the treatment of several types of malignant neoplasms and keeps moving forward.[4] Despite enormous therapeutic advances, most treatments are still offered to prolong and facilitate patient survival, hence called palliative antineoplastic treatment.

In this context of multiple systemic therapeutic options, the oncologist, who has an optimistic nature and often personal difficulty in dealing with situations of finitude, finds himself in the difficult situation of suspending an antineoplastic treatment. The "availability bias,"[5] a mental shortcut that relies on immediate examples that come to mind, for example with the

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memory of anecdotal cases of significant clinical improvement with chemotherapy, probably interferes in the medical decision to try a new cancer treatment. This situation is often stimulated by the patient's inclination to want to be treated and to seek a new source of hope. The communication of the absence of new systemic antineoplastic treatment is often complex, demanding a lot from the oncologist, who may not have had adequate training for this task.[6]

Chemotherapy in the last days of life may cause harm by decreasing quality of life and raising costs, and it does not improve survival times.[7-9] As a result, death within 14 and 30 days of chemotherapy has been used as a quality indicator for cancer care.[10,11] Although not a well-established definition, overly aggressive care is associated with more than 10% of patients who have received chemotherapy in the past 14 days.[12] When a patient receives chemotherapy treatment at the end of life, it suggests that the oncology service has failed to adequately integrate the philosophy of palliative care into cancer care.

There has been a significant advance in oncology support strategies during antineoplastic treatment and after it has ceased. Several clinical trials have shown the benefit of early inclusion of palliative care concomitant to oncologic treatment.[13-17] There are improved health-related quality of life indices, reduced symptoms of depression, improved symptom control, and greater satisfaction with care by patients and caregivers, as well as reduced costs and less aggressive end-of-life care.[18,19] Thus, when integrated early into a service with well-structured palliative care and adequately trained staff, it is possible for patients to receive more time in oncology treatment, including more intensity of treatment, without significant impact on their qualities of life. It is important to note that with the advance of new cancer therapies, for example, with the advent of oral therapies that can be used for a prolonged time and with high efficacy, active and palliative care have blurred boundaries.

In this article, we will didactically divide the oncologist's assessments according to a mnemonic rule of the ABCDE of therapeutic decision-making (Figure 1).

A: **A**dvanced cancer

B: **B**enefits (principle of beneficence)

C: **C**linical conditions and risks (principle of non-maleficence)

D: **D**esire, values, preferences, and beliefs (principle of autonomy)

E: Prognostic **E**stimation

What Is the Disease? (A: Advanced Cancer)

The first step in applying these concepts is to identify whether the disease in question is indeed an advanced and incurable cancer. Throughout this article, we will consider as advanced disease that which is locally recurrent or with distant metastases, not amenable to surgical resection. Thus, the mnemonic rule below was designed to be used where the expected

clinical outcomes of treatment are symptom control, improved quality of life, and/or improved survival times. In early disease cancers, the primary focus is on increasing cure rates and survival times; thus, often with "acceptable" increases in treatment toxicity. In incurable disease, the focus is ultimately on promoting quality of life and, if possible, increasing lifespan.

What Are the Potential Clinical Benefits of This Treatment? (B: Potential Benefits)

This is perhaps the most important step to consider during the process of deciding whether or not to treat a patient with an advanced cancer. The medical literature is extensive regarding new anticancer therapies. However, most clinical trials have not included real-life patients, but rather patients in good clinical condition and not fully representative of the general patient population.[20] When a patient perfectly fits the eligibility criteria of a previous positive clinical trial, the decision about treatment is often easy since the potential benefit can be generalized and explained to the patient during the shared decision process. The difficulty, which often translates into the art of oncology, is treatment decisions in situations outside the contexts of clinical trials, for example, in patients with co-morbidities or inadequate functional performance.

Currently, there are tools developed to help measure the potential benefit of a treatment, such as the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS)[21] and the American Society of Clinical Oncology (ASCO) Value Framework—Advanced Disease.[22] In the ASCO Value Framework—Advanced Disease, for instance, 4 sections are evaluated: Clinical Benefit; Toxicity; Bonus Points; and Net Health Benefit. In the Clinical Benefit section, overall survival (OS), progression-free survival (PFS), and response rate (RR) are measured with distinct weights; the authors suggest multiplying OS, PFS and RR benefits by 16, 11, and 8, respectively. Interestingly, in the Bonus Point section, symptom palliation and treatment-free intervals are measured. These tools were developed considering the vast universe of new cancer therapies, with both patients' and healthcare systems' economic impact. Although the tools cited are extremely useful in defining therapeutic protocols, they are probably of little use in real-life shared decision-making processes.

Palliative antineoplastic treatments can vary significantly depending on the economic region of the world in which a patient lives, and the type of access to public or private healthcare services. Factors such as the availability of specific drug protocols, medical expertise, and funding can impact the type and quality of care provided.[23] In some countries or regions, access to palliative antineoplastic therapies may be limited, while in others, patients may have a wider range of treatment options available to them.[24] In addition, racial and ethnic minorities are underrepresented in oncology clinical
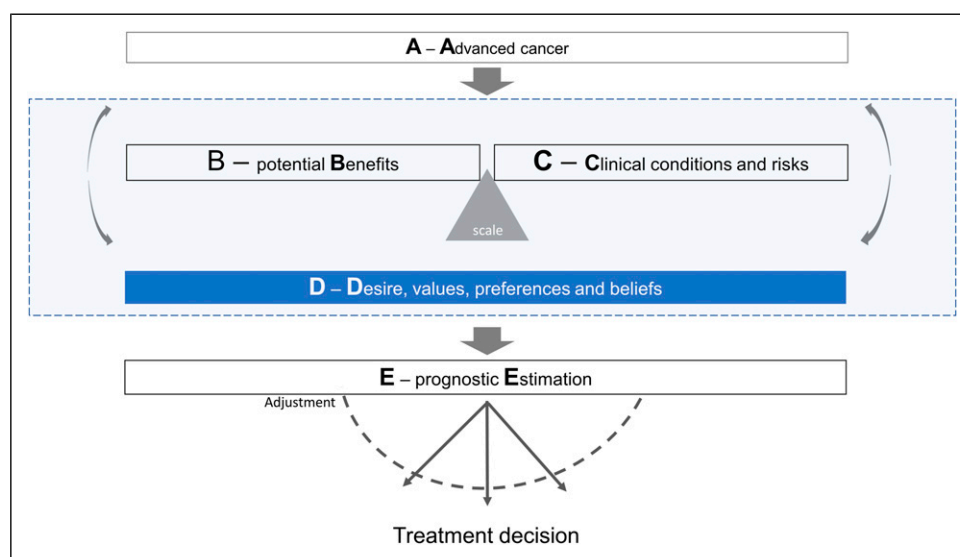
Figure 1. Conceptual flowchart of the suggested therapeutic decision-making process. *A: Advanced cancer.* The first step in applying these concepts is to identify whether the disease in question is indeed an advanced and incurable cancer. *B: potential benefits.* Discuss and share with the patient the potential benefits of the antineoplastic treatment. *C: clinical conditions and risks.* Discuss and share with the patient the clinical conditions (functionality, comorbidities) and the potential risks of the antineoplastic treatment. *D: desire, values, preferences, and beliefs.* Identify and understand patients' desires, values, preferences, and beliefs. *E: prognostic estimation.* The prognostic estimation may function as an "adjust" for the antineoplastic treatment decision-making.

trials, potentially reducing the generalizability of findings.[25] These differences highlight the importance of considering individual circumstances when determining the most appropriate treatment plan for patients with advanced cancer.

In daily practice, what the clinical oncologist needs is to know the details of clinical trials that guide his/her patients' treatment indications and know how to conduct shared decision-making using good communication skills. In addition to defining the potential benefit of treatment based on the literature using tools that measure value in health care, it is of utmost importance to identify the value of treatment from the patient's perspective.[26]

What Are the Clinical Conditions and Potential Risks of the Treatment in Question? (C: Clinical Conditions and Risks)

Weighting the risks and benefits of prescribing an antineoplastic treatment for older adults, with comorbidities, or borderline performance status is challenging for the oncologist.

Previous studies in the general population, have suggested an association between measures of physical performance and all-cause mortality.[27,28] As in the general population, physical functioning is associated with the prognosis of patients with advanced cancer.[29-31] One of the traditional ways of evaluating the functionality of a cancer patient is through the measurement of his functional performance by means of the Karnofsky Performance Status[32]

and the Eastern Cooperative Oncology Group Performance Status (ECOG-PS).[33]

Most clinical trials have included patients in better clinical condition, with ECOG-PS 0 or 1 and, in less than 10% of the time, ECOG-PS of 2[30]. In the meta-analysis by Cheng et al,[34] only one clinical trial out of 62 evaluated (<2%), included patients with an ECOG-PS of 3. Thus, day-to-day therapeutic decisions in patients with poor functional conditions (ECOG-PS 2 or 3) are mostly made outside of clinical trial best evidence. While prognosis is clearly associated with patient performance status (PS), the benefit of cancer treatment may not be related. The relative benefit of treatment appears to have no interaction with performance status, both in studies that included older treatments regimens[30] and studies with targeted drugs included.[34] In contrast, non-small cell lung cancer patients with impaired PS status were, on average, twice less likely to achieve a clinical response when exposed to immune checkpoint inhibitors when compared with ECOG-PS ≤1 population.[35]

The association of antineoplastic treatment with the risk of adverse events in the different PS subgroups needs to be further explored in new studies. Severe nausea and vomiting, for instance, were much more pronounced in ECOG-PS 2 patients than in ECOG-PS 0 to 1 patients.[30] In addition, it is important to remember that cancer patients may have their PS influenced by the cancer itself, but also as a function of some comorbidity. Such information can be important for the oncologist while defining the treatment. For example, in patients with cancer symptoms and reduced PS, antineoplastic treatment may be indicated in an attempt to therapeutic response, improvement of symptoms and PS; however, patients with

poor PS due to comorbidity may even worsen the PS by oncologic treatment.

Another variable that interferes in the decision about cancer treatment is advanced age and the consequent vulnerability of the patient. In patients aged 65 and older, receiving antineoplastic treatments, geriatric assessment (GA) should be used to identify vulnerabilities or geriatric impairments. The GA comprises the evaluation of functional status, falls, comorbidities, depression, social activity/support, nutritional status, and cognition.[36] Elderly cancer patients are particularly prone to "over-treatment," with a high likelihood of complications/toxicity, or "undertreatment," that is, not receiving desirable treatment that they would be fit for, for fear (on the part of the oncologist or the patient themselves) of complications.[37,38] Furthermore, traditional oncology performance measurement tools, such as KPS or ECOG-PS, are not accurate in predicting risk of complications in elderly patients.[39]

To assist the oncologist, several practical tools are available. Among the tools that can provide estimates of the risk of chemotherapy toxicity are the Cancer and Aging Research Group (CARG)[39,40] and the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH)[41] toxicity tools (Table 1).

The Geriatric 8 (G8),[42] the Vulnerable Elders Survey-13 (VES-13),[43] the abbreviated Comprehensive Geriatric Assessment (aCGA),[44] the Groningen Frailty Index (GFI),[45] and the Flemish version of the Triage Risk Screening Tool (fTRST)[46,47] are among the screening tools that have been associated with adverse outcomes. These tools should be used to identify frail and/or vulnerable patients who are most likely to benefit from a geriatric assessment.[48] The G8 and the VES-13 are the screening tools with the most scientific evidence for clinical use[49] (Table 1).

Regardless of PS and age, the presence of significant comorbidities is of utmost importance in the setting of antineoplastic treatment, influencing the patient's course of disease and the choice of antineoplastic treatment.[50–54] In 1987, Charlson and colleagues[55] developed a method to classify nineteen patient comorbidities to predict risk of death within 1 year of hospitalization. The comorbidities represent different weights in the final score (Table 2), ranging from 1 to 6. Since then, the Charlson Commorbidity Index (CCI) has been the most widely used tool in the studies to measure the impact of comorbidities on clinical outcomes of patients with different cancer types (for a detailed review, please see 56).

Considering that a comorbidity measure developed or adapted for a specific disease population is likely to perform better than a generic score,[57] the CCI has been further reviewed and adapted for use in oncology populations. Of note, the original CCI includes as comorbidities some hematological neoplasms and metastatic cancer. Thus, in 2000, a cancer-specific National Cancer Institute Comorbidity Index (NCI-CI) was developed by using SEER derived breast and prostate cancer cases cohorts, excluding solid tumors, leukemias, and lymphomas as comorbid conditions.[58] Subsequently, the NCI comorbidity score evolved into the NCI Combined Index Models, which outperformed the original CCI in predicting 2-year survival in cancer patients.[59]

Another tool for assessing the impact of comorbidities is the Elixhauser comorbidity index (ECI), which includes a total of 30 comorbidities.[60] Originally, each comorbidity has equal weight; modifications of the ECI with different weights for each comorbidity have already been described.[61,62] A previous systematic review[63] found that the ECI performs better than the CCI in predicting mortality beyond 30 days. It has already been adapted for use in cancer patients,[64] achieving higher C-Index values when compared to the NCI Combined Index Model.

In patients with lung cancer, the Scottish Comorbidity Scoring System (SCSS),[65] which classifies 9 commodities according to their severity (nil: 0; low: 1–6; severe: 7 or more), proved more useful than the CCI in predicting overall survival in patients with localized (stages I–IIIA) and advanced disease (stages IIIB and IV).

As mentioned earlier, the most commonly used way to assess comorbidities in studies is through the CCI or one of its variations. However, there is no gold standard instrument for this.[66] As a practical suggestion, there are easy-to-use Excel applications that can be obtained for free and used to calculate comorbidity scores.[67,68] Despite the availability of the tools mentioned, in practice, the oncologist generally evaluates comorbidities in an individualized manner within a typical anamnesis. When planning systemic antineoplastic therapy, hepatic, renal, cardiovascular, and hematologic functions need to be carefully considered. In addition, uncontrolled active infections should be ruled out before the initiation of antineoplastic therapies since most of treatments can course with a drop in WBC and neutrophil levels and changes in the immune system.

Although not well defined, the decision to treat with antineoplastics can differ significantly among various medical oncology subspecialties, particularly those that specialize in specific tumor types, such as breast, gynecologic, lung, or colorectal vs those that treat a wide range of tumors in general oncology. Interdisciplinary communication and collaboration among all involved disciplines, including palliative care, general practitioners, and geriatric oncology, are crucial to ensuring that patients receive the most appropriate care for their unique circumstances.[69–71]

Patients with hematological malignancies carry a significant burden of illness, often receiving more aggressive end-of-life treatments and experiencing a high level of symptom distress. Despite this, they tend to underutilize palliative care, especially those with leukemia.[72,73] It has been reported that hemato-oncologists are more inclined than oncologists to prescribe systemic therapies that carry moderate toxicity and do not confer any survival benefits to patients who present low performance status and an expected survival of one month.[74]

Table 1. Validated Geriatric Assessment Tools.

Tool	Aim	Variables	How to use
CARG[37,38]	Toxicity prediction	11 items: 5 geriatric assessment items and 6 items from routine daily practice (tumor type, treatment, and laboratory values)	Scoring system ranging from 0 to 19 Risk score: Incidence (%) of grades 3–5 chemotherapy toxicity in older adults at low (0–5 points) = 30%; intermediate (6–9 points) = 52%; or high risk (10–19 points) = 83%
CRASH[39]	Toxicity prediction	8 items divided in 2 scores: Hematological (H) (diastolic blood pressure, IADLs, LDH, Chemotox score) and non-hematological (NH) (ECOG, MMSE, MNA, Chemotox score)	The predictors of H toxicity were IADLs, lactate dehydrogenase, diastolic blood pressure, and Chemotox. Risk categories: low, 7%; medium-low, 23%; medium-high, 54%; and high, 100%, respectively. The predictors of NH toxicity were ECOG, MMSE, MNA, and Chemotoxicity. Risk categories: low, 33%; medium-low, 46%; medium-high, 67%; and high, 93%, respectively.
VES-13[39]	Geriatric screening tool	13 items, including age, self-rated health, limitations in physical function, and disability	Sensitivity and specificity of 68.7% and 74.3%, respectively. VES-13 score ≥3 predicts a 68% risk of abnormality in 2 or more domains on subsequent CGA and is associated with a 4.2-fold increased risk of death and functional decline.
G8[40]	Geriatric screening tool	15 items, including food intake, weight loss, BMI, mobility, neuropsychological problems, medication intake, and age	Sensitivity and specificity of 76.5% and 64.4%, respectively. A score ≤14 is associated with ≥80% risk of abnormalities in one or more domains on subsequent CGA.
aCGA[41]	Geriatric screening tool	15 items that were divided into 4 domains: ADL (3 items), IADL (4 items), MMSE (4 items), and GDS (4 items)	Each domain has an individual cutoff point. Two positive "yes" items on the aCGA indicates the use of the full GDS (specificity .89; sensitivity .81). In the ADL domain, a positive item for "need for assistance" should be screened using the entire instrument. In the IADL topic, a positive item for "need for assistance" should be screened using the entire instrument. For the dementia topic, a score ≥6 indicates screening with the MMSE (sensitivity .91; specificity .82)
GFI[42]	Geriatric screening tool	15 items, including physical (mobility, fatigue, vision, and hearing), cognitive, social (emotional isolation), and psychological (depression and anxiety) domains	A cutoff of ≤4: Absence of a geriatric risk profile
fTRST[43,44]	Geriatric screening tool	5 items assessing the presence of cognitive decline (yes, 2 point), living alone or without help (yes, 1 point), reduced mobility or falling (yes, 1 point), hospitalization in the last 3 months (yes, 1 point), and polypharmacy (yes, 1 point)	The total score ranges from 0 to 6. Cutoff ≥1 point

Abbreviations: CARG, Cancer and Aging Research Group; CRASH, Chemotherapy Risk Assessment Scale for High-Age Patients; VES-13, The Vulnerable Elders Survey; G8, Geriatric 8; SAOP3, Senior Adult Oncology Program 3 screening questionnaire; fTRST, Flemish version of the Triage Risk Screening Tool; GFI, Groningen Frailty Index; aCGA, Abbreviated Comprehensive Geriatric Assessment; IADLs, Instrumental Activities of Daily Living; ADL, Activities of Daily Living; LDH, Lactase Dehydrogenase; ECOG, Eastern Cooperative Oncology Group; H, Hematology; NH, Non-Hematology; MMSE, Mini Mental Status Examination; MNA, Mini Nutritional Assessment; CGA, Comprehensive geriatric assessment; BMI, Body Mass Index; GDS, Geriatric Depression Scale.

Physicians without specialized knowledge in palliative medicine tend to make more aggressive decisions regarding end-of-life care, such as administering higher levels of intravenous hydration, nasogastric tube insertion, and blood transfusions.[75] Additionally, a previous systematic review found that younger and less experienced oncologists were more likely to continue palliative antineoplastic treatment.[6]

In the decision to treat with antineoplastics, and particularly in the choice of the type of antineoplastic, the oncologist needs to measure the possible adverse events of the treatment, even if not severe enough to be life-threatening, but that may interfere with the quality of life of the patients. For example, a professional pianist with peripheral neuropathy may have to stop work. Similarly, patients who need their body image intact to work (such as models, TV journalists) will strongly wish to avoid alopecia. Thus, just as treatment needs to be customized considering the molecular characteristics of the tumor, it is also necessary to customize treatment considering the treatment's potential interference with the patient's personal and work life.

Table 2. Classic Comorbidity Assessment Tools and its Weighed Cancer-Specific Versions.

Comorbid Conditions	CCI[52]	NCI-Breast[56]	NCI-Prostate[56]	NCI-Colorectal[56]	ECI[57]	ECI-Breast[61]	ECI-Prostate[61]	ECI-Lung[61]	ECI-Colorectal[61]
Myocardial infarction	1	0.40	0.05	0.28					
Congestive heart failure	1	0.85	0.87	0.84	1	7	9	1	3
Cardiac arrhythmias					1				
Peripheral vascular disease	1	0.22	0.36	0.28	1	4	3	2	2
Cerebrovascular disease	1	0.71	0.27	0.55					
Hypertension					1	-1	-1	0	0
Fluid and electrolyte disorders					1	2	4	0	3
Anemia (Blood loss)					1	2	-6	0	1
Deficiency anemia					1	1	2	0	1
Dementia	1	1.19	0.78	0.60					
Chronic pulmonary disease	1	0.47	0.73	0.47	1	5	5	3	5
Pulmonary circulation disorders					1	5	−2	3	1
Connective tissue disease	1	0.75	0.09	−0.02	1	0	0	3	1
Peptic ulcer disease	1	0.23	−0.25	0.08	1				
Liver disease					1	6	−4	0	6
Mild liver disease	1	2	3						
Moderate or severe liver disease	3				1	6	−4	0	6
Diabetes	1	0.45	0.24	0.44	1	3	2	0	1
Diabetes (with end-organ damage)	2	0.02	0.44	0.30	1	-1	2	1	2
Hemiplegia (or paraplegia)/Paralysis	2	0.21	0.39	0.30	1	6	3	2	-2
Neurologic or degenerative disorder					1	5	2	3	2
Psychoses					1	4	4	1	2
Depression					1	2	0	2	3
Renal failure					1	3	1	2	1
Moderate or severe chronic renal failure	2	1.19	0.68	0.97					
Any tumor without metastasis	2				1				
Metastatic solid tumor	6				1				
Leukemia	2								
AIDS/HIV	6				1				
Lymphoma	2				1				
Previous malignancy									
Hypothyroidism					1	1	−4	1	1
Coagulopathy					1	2	0	−1	2
Valvular disease					1	1	1	1	1
Obesity					1	−6	−7	−1	−3
Weight loss					1	3	1	3	3
Alcohol abuse					1	2	9	0	−1
Drug abuse					1				

Abbreviations: CCI, Charlson Comorbidity Index; NCI, National Cancer Institute Combined Index; ECI, Elixhauser comorbidity index.

D: How can we identify the Patients' Wishes, Preferences, Beliefs, and Values That May Influence the Choice of Treatment? (D: Desires, Values, Preferences, and Beliefs)

In our mnemonic model of therapeutic decision, after evaluating parts B and C, which basically defines a decision scale (risks vs benefits), we move to the next phase that uses the patient's perception of the treatment, taking into consideration their personal wishes, values, and beliefs; part D is broad and interferes with the discussion on parts B and C (Figure 1). Here it is important to discuss ways of extracting such information from the patient. The question "do you want to try a new treatment?" is generally inappropriate, as most patients wish to live and be cured and will answer the question in the affirmative.

Patients with cancer must cope with a variety of stressors, including the need for treatment on an urgent basis, the management of adverse effects of treatment, the sharing decision-making processes, the numerous physical and emotional challenges while dealing with a life-threatening illness, and having to tolerate uncertainty regarding their future.[76,77] Thus, one cannot expect patients to be consciously positive if they don't have a space to meet and talk about their care preferences and express their distress, or without providing them the necessary time to adapt to the cancer experience and enhance their repertoire of coping strategies,[77] a gap that can be reduced with the help of an Advance Care Planning (ACP).

ACP is a process of planning for future health and personal care that helps patients make decisions and identify their values and preferences for care at a time when they are unable to make or communicate their decisions. This type of planning is intended to align the care the patient will receive with their preferences and priorities.[78] ACP develops in an interactive and communicative process where patients, healthcare staff, and family members have conversations about preferences for care, particularly those at the end-of-life. These preferences may even be recorded in a legal document, called advance directives.[79,80]

Advance care planning is a crucial aspect of cancer care, especially when making decisions about new anticancer treatments. A previous ACP can help patients and their families make informed decisions about treatment options, considering the potential benefits and harms of each intervention, as well as the patient's overall health status and prognosis. However, patients with advanced cancer often have not previously participated in ACP discussions. In such situations, serious illness goals of care conversations need to be conducted by trained oncologists. While ACP focuses on preparing the patient for future healthcare decisions, goals of care discussions focus on current healthcare decision-making.

In order to help patients with advanced cancer articulate their goals of care, oncologists need to assess patients'

knowledge of their disease and prognosis. Often, patients with advanced cancers undergoing chemotherapy report an inaccurate perception of curability.[81,82] Prognostication is a dynamic and multi-step process encompassing the sequence of prognostic prediction, prognostic disclosure, prognostic awareness, prognostic acceptance, and prognostic-based decision-making.[83] In fact, when patients are aware of their disease stage and prognosis and, preferably, emotionally accept the situation, the clinical decisions to treat or not to treat them are facilitated by sharing decisions in a mature way and with potentially less distress.

Below are some examples of open, in-depth questions, oncologists may use to identify and understand the patient's wishes, preferences, beliefs, and values[84–86]:

Identifying Patient Values

"What does 'living well' mean to you? What are your goals right now?"

"What are your biggest fears and worries about the future with your health?"

"What gives you strength as you think about the future with your illness?"

"What abilities are so critical to your life that you can't imagine living without them?"

"How much does your family know about your priorities and wishes?"

Exploring Disease Understanding and Treatment Goals

"What are your most important goals if your health situation worsens?"

"What do you understand about the current status of your illness?"

"What is your understanding now of where you are with your illness?"

"How much information about what is likely to be ahead with your illness would you like from me?"

Identifying Future Care and Treatment Preferences

"If you become sicker, how much are you willing to go through for the possibility of gaining more time?"

"Tell me a little bit about your main future wishes"

"Would you like to actively participate in your advance care planning?"

"When you no longer have the ability to make decisions, what care or treatment would you not want in your end-of-life process?"

To understand the profile of patient care preferences and to serve as a stimulus for further discussion about cancer treatment, we have been using in practice the following trade-off item from a previous publication[81]: "If you could choose only one of the options, would you prefer... (A): a treatment that was designed to prolong life as much as possible, even if the treatment caused more pain and discomfort; or (B): a care plan to relieve pain and discomfort as much as possible, even if it meant not living as long." Other ways of assessing health care preference in a similar way, particularly in the elderly with cancer, have been described.[87,88]

To take into consideration the wishes and values of patients is to respect their autonomy, and consequently, their dignity.[89,90] The conduct of dignity-promoting activities in the process of illness and end-of-life of cancer patients brings to the family members the possibility of discussions about the resolution of pending issues, whether affective, financial, and even bureaucratic (insurance, contracts, inventories), deliberation of care for dependents, better development of resources for coping with the imminent loss of loved ones, and elaboration of the bereavement process.[91]

The practical use of tools that allow the health team to identify the wishes of patients during the dying process and subsequent development of conducts that promote their dignity, is a promising strategy to improve the care of cancer patients. A potentially useful strategy to facilitate end-of-life conversations is the Go Wish Cards Game (GWCG), composed of 36 cards, which display a variety of end-of-life wish preferences. The cards are separated into 3 piles considering the ten not so important, the ten more or less important, and the ten very important wishes; the most important wishes are further discussed with the patients. The GWCG method is one of the ways of optimization in dignity therapy for patients in advanced disease process. The use of the cards brings important ways to initiate dialogues and broaden engagements between patient, family members, and multidisciplinary team, through simple vocabulary and variety of possible wishes that extend to the essence of well-being of the human being.[92,93] A study carried out with patients with advanced cancer compared a random wish list developed by the patients and the GWCG and found that 62% of the patients preferred the GWCG for its ease of understanding and for presenting a wider range of wish options. Additionally, it was easy to apply.[94]

In general, the oncologist needs to be open and trained to identify patients' wishes, values, beliefs, and preferences. The introduction of processes into routine care (such as ACP and goals of care discussions) and the use of practical tools such as the GWCG can be extremely helpful to the oncologist in the therapeutic decision process. It is important to note that the treatment decision does not necessarily have to occur in a single moment but is often the result of sequential medical consultations.

E - What Is the Patient's Estimated Lifetime? (E: Prognosis Estimation)

After evaluating the potential benefits (part B), the clinical conditions/risks of the treatment (part C), and the importance of a new therapeutic attempt in the patient's view (part D), it is essential to "adjust" the clinical decision considering the patient's life expectancy (part E) (Figure 1). As mentioned earlier, the parts are divided here from a didactic point of view. Thus, prognostication is intrinsically related to part D and can be omitted from the process. We suggest part D as an adjustment in the shared decision, particularly in situations where treatment decisions are incongruent from the oncologist's point of view. For example, patients where it is proposed to treat with new chemotherapy, but the estimated prognosis is only a few months.

The prognosis estimation is not able to independently establish the indication of a new treatment, however it can assist in the decision making. Furthermore, expectations are not usually communicated to patients routinely, but only in specific situations. The prognosis is somewhat dynamic and can be modified by the treatment itself.[95] We strongly suggest that its communication, when provided to the patient, should be in the form of intervals and never with specific time values or mean/medians, such as "hours to days," "days to weeks," "weeks to months," "months to years."

Clinical Prediction of Survival

Among the strategies for estimating the prognosis of an advanced cancer patient, one of the most classic and instituted ways is the clinical prediction of survival (CPS), in which the opinion of the health professional, mainly the physician, is considered. It is often overestimated, due to excessive optimism in predicting the survival, particularly those patients who die early in the terminal phase and could benefit from earlier palliative care.[96]

The low concordance between clinical predictions and actual survival times is evidenced in systematic reviews of the literature, with 83% of prediction errors being overestimated by physicians[97] and an estimate of 4 weeks beyond observed in 27% of cases.[98] The accuracy of physicians in estimating the prognosis of advanced cancer patients in survival intervals, for example, varies around 60% and the professional's experience does not seem to interfere on the accuracy of prediction.[99] Even palliative care specialists are unable to predict survival in 32% of cases if a patient is alive or dead at 4 weeks.[100]

Functionality Scales

The functionality assessment is another way to predict prognosis, using functional performance scales, such as the Eastern Cooperative Oncology Group Performance Status (ECOG-PS),[33] the Karnofsky Performance Status (KPS)[32] and

the Palliative Performance Scale (PPS).[101] These instruments have been widely used as prognostic tools, with an important role in the scenario of survival estimates, through the interpretation of a patient's dependence on the environment in which they live, measuring their ability to perform activities of daily living, without assistance.

Symptoms of Advanced Disease and Laboratory Parameters

With the awareness of the potential limitations of functional performance scales (such as, low inter-observer reproducibility and cross-sectional evaluation), the assessment of clinical symptoms in combination with KPS and physicians' clinical estimates may improve survival prediction. Symptoms such as anorexia, cachexia, weight loss, dysphagia, and pain may be independently associated with a worse prognosis in advanced cancer patients. In exclusive palliative care setting, the mental confusion, fatigue, cachexia, weight loss, dyspnea, dysphagia and nausea predict a shorter survival.[102] It is important to point out that the clinical assessment of symptoms is also subjective and often influenced by psychosocial factors, which leads to some inaccuracy in its measurement, even with the use of visual scales.[103,104]

Laboratory parameters are possible prognostic markers in patients with advanced-stage cancer. The presence of leukocytosis, as well as lymphopenia, is associated with a worse prognosis in patients with advanced cancer.[105] Lactic dehydrogenases (LDH), a serum marker that rises in cases with high disease volume, and the c-reactive protein, a marker related to inflammation, are more nonspecific, but in the context of advanced cancer they can be associated with progressive disease.[106,107] Hypoalbuminemia, in addition to reflecting the nutritional status of patients, also expresses a negative influence on the prognosis of critically ill patients.[105]

Prognostic Tools

Knowing the limitations of predicting survival based on clinical estimates by physicians, assessment of symptoms and biochemical parameters, there is robust evidence that the combination of all parameters in one model may improve the prediction of survival in advanced cancer patients.[96] Prognostic models have been created in the palliative care setting, improving the accuracy, and helping healthcare professionals to plan the patient journey.

The Palliative Performance Scale (PPS),[101] Palliative Prognostic Score (PaP),[108,109] Palliative Prognostic Index (PPI),[110] Objective Prognostic Score (OPS)[111] and Prognosis in Palliative Care Study Predictor (PiPS)[112] were developed and validated for patients with few months of life expectancy. In contrast, the modified Glasgow Prognostic Score (mGPS),[113,114] the PRO-NOPALL prognostic tool,[115] the Spanish Prognostic Nomogram (SPN),[116] the Barretos Prognostic Nomogram (NPB)[117] and the HAprog (clinical and full versions)[118] were developed in patients

with advanced cancer with an expectation of several months of survival (Table 3). It is interesting to note that the prediction accuracies increase the closer the patient is to the end of life.

There may be a myriad of combinations between prognostic variables; each model has its peculiarity, according to the profile of patients evaluated. However, some variables are more frequently contemplated, such as the functional status of the patient. Almost all the main models, regardless of life expectancy, include performance status as a clinical variable, with KPS being the most used way. Only models related to a shorter life expectancy (days to weeks) include symptoms and clinical signs as prognostic factors, with "delirium," "dyspnea," and "anorexia" being the most frequent observed.

Inflammatory laboratory variables were included in some prognostic models, among which "total leukocytes," "serum albumin," and "LDH" stand out as the most frequently related. Among these models with longer life expectancy, only the NRF and HAprog clinical version models did not assess laboratory variables.[118,119] On the other hand, the mGPS is the only model that presents only laboratory variables in its composition (c-reactive protein, albumin), however better accuracy is achieved when evaluated together with the ECOG-PS.[113,114] Laboratory variables can indeed increase the prognostic ability of a tool, but it can be a barrier to its applicability in the clinical routine, regarding the request for complementary tests in patients under palliative care.

The quick access to prognostic tools for use in clinical practice is essential. *PredictSurvival.com* is an online platform, free to use, which includes grouped classic prognostic tools, being particularly useful for cases of patients in the last 6 months of life.[120] Its use by health professionals has increased prognostic confidence and accessibility to discuss the prognosis with patients.[121] In this same context, the HAprog models have been transcribed into a digital version for use in smartphones.[118] Interestingly, in addition to calculating the probabilities of survival at 30, 90, and 180 days, HAprog shows the probable survival times in days in the expected, worst-case, and best-case scenarios. The practical implication of these results still needs to be evaluated in subsequent studies.

Despite the availability of validated predictive tools in the current literature, there are still barriers to their use in daily clinical practice. Knowing the importance of estimating an accurate prognosis, choosing which tool to use for each patient, knowing how to interpret and communicate the estimated survival value and managing time during patient care are issues that must be still on the discussion.[120,122] It is important to emphasize that the use of a prognostic tool does not have the intention of standardizing or "mechanizing" the process of evaluating the patients' survival, but it increases the clinical evaluation of the physician with less subjectivity and greater accuracy.

Future Perspective

Communicating difficult news in oncology is a complex and stressful task for oncologists[123] that should be taught, learned,

Table 3. Prognostic Tools for Use in Advanced Cancer Patients.

Prognostic tool	Life Expectancy	Patient Profile	Variables (N, Description)	Practical Implications
PPS[92]	Weeks to days	Patients under palliative care	1: Performance status	KPS adaptation is ideal application for use in palliative care patients, especially those with worse clinical conditions
PaP[99]	Weeks to days	Cancer patients under exclusive palliative care and a life expectancy lower than 30 days	6: KPS, dyspnea, anorexia, clinical prediction of survival, leukocytes, lymphocytes	Used in the last month of patient's life. Clinical variables of symptoms and clinical prediction of survival are considered
D-PaP[100]	Weeks to days	Cancer patients under exclusive palliative care and a life expectancy lower than 30 days	7: KPS, dyspnea, anorexia, delirium, clinical prediction of survival, leukocytes, lymphocytes	Similar to PaP, with the inclusion of "delirum" as a variable, which slightly improved the prognostic accuracy of the tool
PPI[100]	Weeks to days	Advanced cancer patients and a life expectancy lower than 3 weeks	5: KPS, dyspnea, anorexia, delirium, edema	Similar to D-PaP but without laboratory variables and with the inclusion of the "edema" variable. There is an alternate variation of this model that substitutes KPS for ECOG (PPI-ECOG)
OPS[101]	Weeks to days	Advanced cancer inpatients for hospice care in terminal stage and a life expectancy lower than 3 weeks	7: ECOG, oral intake, dyspnea, leukocytosis, serum bilirubin, serum creatinine, and lactate dehydrogenase	Only model that uses non-inflammatory laboratory variables
mGPS[103,104]	Months	Advanced cancer patients and a life expectancy lower than 3 months	2: C-reactive protein and albumin	The combination of 2 laboratory variables could represent the patient's inflammatory state, however without evaluating clinical variables. It can be applied to patients with a longer life expectancy, but its use in conjunction with the ECOG-PS is suggested for greater accuracy.
NRF[109]	Months	Cancer patients and a life expectancy lower than 60 weeks	3: KPS, site of primary neoplasm (breast vs non-breast), site of metastases (bone vs non-bone	Specific profile of patients from a radiotherapy service.
PRONOPALL[105]	Months	Advanced cancer patients and a life expectancy lower than 2 months	4: KPS, number of distant metastasis sites, albumin, lactic dehydrogenase	Dichotomic variables. Results presented in 3 groups of possible survival at 2 months
SPN[106]	Months	Advanced cancer patients in exclusive palliative care and a life expectancy lower than 60 days	4: ECOG, time from diagnosis to palliation, lymphocytes, albumin, lactic dehydrogenase	Functional performance status, duration of illness, and laboratory variables
BNP[107]	Months	Advanced cancer outpatients when referred for the first time to palliative care and a life expectancy lower than 180 days	5: Gender, KPS, presence of distant metastases, leukocytes, albumin	The only evaluated model that uses gender as a variable and was developed for patients in an outpatient setting. Presents the KPS as a continuous variable, but restricted above 40%
HAprog full version[108]	Months	Advanced cancer outpatients when referred for the first time to palliative care and a life expectancy lower than 180 days	6: Gender, ECOG, sites with distant metastases, presence of locoregional disease, leukocytes, albumin	Refinement of the BPN with the replacement of KPS by ECOG and optimization of the variable "metastasis" (previously evaluated in a dichotomous way). In addition, an application for use on smartphones was developed.

(continued)

Table 3. (continued)

Prognostic tool	Life Expectancy	Patient Profile	Variables (N, Description)	Practical Implications
HAprog clinical version[108]	Months	Advanced cancer outpatients when referred for the first time to palliative care and a life expectancy lower than 180 days	5: Gender, ECOG, sites with distant metastases, presence of locoregional disease, ongoing antineoplastic treatment	Variation of the HAprog full version model, without considering laboratory variables and including ongoing antineoplastic treatment

Abbreviations: PPS, Palliative Performance Scale; PaP, Palliative Prognostic Score; D-PaP, Palliative Prognostic Score with Delirium; PPI, Palliative Prognostic Index; OPS, Objective Prognostic Score; mGPS, Modified Glasgow Prognostic Score; NRF, Number of Risk Factors; SPN, Spanish Prognostic Nomogram; BPN, Barretos Prognostic Nomogram; ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Status.

and retained. The SPIKES protocol,[124] the elements of which are Setting, Perception, Invitation, Knowledge, Emotions, and Strategy, is the most commonly used framework in the education of medical students, residents, and oncologists.[125] A recent systematic review[126] identified 3 communication models validated through randomized clinical trials; that is, the Serious Illness Conversation Guide,[127] the 4 Habits Model,[128] and the acronym ADAPT.[129] Another very useful mnemonic when discussing goals of care is the framework REMAP (Reframe, Expect emotion, Map outpatient goals, Align with goals, and Propose a plan).[130]

In this article, we present the ABCDE mnemonic rule of therapeutic decision-making, which can assist oncologists not only in the direct communication process but also with a conceptual model of decision-making to be considered and discussed with patients with far advanced cancers when deciding about continuing or discontinuing antineoplastic treatment during the shared decision-making process. Future studies are needed to test whether new communication skills training programs that include our decision model are able to reduce aggressive end-of-life treatment and promote decision-making that aligns with the preferences of well-informed patients regarding their disease and prognosis.

Conclusions

The therapeutic decision process of whether or not to treat patients with advanced cancer with systemic antineoplastic therapies is complex. Oncologists need to know in detail the therapeutic protocols to which they will submit their patients, mainly its potential clinical benefits and risks. In addition, they need to know how to capture and adequately comprehend their patients' wishes, values, and personal beliefs. Accurate prognostic estimates can also help in "fine-tuning" therapeutic decisions.

Appendix

Abbreviations

aCGA	Abbreviated Comprehensive Geriatric Assessment
ACP	Advance Care Planning
ALK	Anaplastic lymphoma kinase
ASCO	American Society of Clinical Oncology
BRAF	B-rapidly accelerated fibrosarcoma protein
CARG	Cancer and Aging Research Group
CCI	Charlson Commorbidity Index
CPS	Clinical prediction of survival
CRASH	Chemotherapy Risk Assessment Scale for High-Age Patients
ECI	Elixhauser comorbidity index
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
ESMO-MCBS	European Society for Medical Oncology Magnitude of Clinical Benefit Scale
FGF	Fibroblast growth factor
fTRST	Flemish version of the Triage Risk Screening Tool
G8	Geriatric 8
GA	Geriatric assessment
GFI	Groningen Frailty Index
GWCG	Go Wish Cards Game
HER2	Human epidermal growth factor receptor 2
KPS	Karnofsky Performance Status
LDH	Lactic dehydrogenases
mGPS	Modified Glasgow Prognostic Score
NCI-CI	National Cancer Institute Comorbidity Index
NPB	Barretos Prognostic Nomogram
NRF	Number of Risk Factors
OPS	Objective Prognostic Score
OS	Overall survival
PaP	Palliative Prognostic Score
PARPi	ADP ribose polymerase inhibitors
PFS	Progression-free survival
PI3K	Phosphoinositide-3 kinase
PiPS	Prognosis in Palliative Care Study Predictor
PPI	Palliative Prognostic Index
PPS	Palliative Performance Scale
PTEN	Phosphatase and tensin homolog deleted on chromosome 10
RR	Response rate
SCSS	Scottish Comorbidity Scoring System

SPN	Spanish Prognostic Nomogram
VES-13	Vulnerable Elders Survey-13
WBC	White blood count

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