Why do our patients get chemotherapy until the end of life?

the patient

Some years ago, I treated a 21-year-old woman. During her first pregnancy, an enlarging mass appeared in her right leg. Diagnostic procedures done after delivery indicated that she had alveolar rhabdomyosarcoma. She was referred to the cancer center for isolated limb perfusion, which was deemed impossible due to inguinal masses encountered during the attempt to canalize the femoral vessels. A computed tomography scan showed peripheral micronodules in both lungs, after which she was referred to the medical oncology department for systemic chemotherapy. By then, the primary tumor was a fungating mass requiring morphone for pain control. Treatment with cyclophosphamide, doxorubicin and vincristine led to a prolonged hospital admission for bacterial sepsis, during which she was visited by her husband daily late after work and on Sundays by her family and the baby. On the subsequent cycle, and despite reduced chemotherapy doses, she again experienced severe hematological toxicity and no antitumor effect or decreased requirement of narcotics. Next, single-agent doxorubicin was administered in the outpatient clinic as an attempt to preserve quality of life. Still no antitumor or symptom response was achieved and multiple hospital admissions due to hematological toxicity ensued. Eventually, ifosfamide was prescribed in progressively lower doses due to increasing hematological toxicity but still without clinical benefit. She finally died of fungal sepsis, 3 months after being referred to the medical oncology department.

the problem

This case illustrates therapeutic futility at the end of life. Why are we not ceasing chemotherapy when it is useless, toxic, logistically complex and expensive? Are we prescribing chemotherapy until too late in solid tumor patients’ lives? Medical oncologists have overly optimistic predictions and, sometimes excessive, treatment-prone attitude and they are criticized by other health care providers for this. Increasingly, patients, their families, advocacy groups, policy makers, journalists and society at large dwell on this topic, which is a perplexing conundrum, because sometimes they are the ones demanding not to stop aggressive systemic anticancer treatments. There is a growing culture of awareness toward preserving quality of life, palliative care, symptom-directed care, hospice referral and end-of-life issues regarding terminal cancer patients. Sadly, this issue is gaining momentum, not because oncologists are questioning their practice but because health care costs are soaring. Whatever the motive, the reasons for administering chemotherapy at the end of life should be known. Striking a balance is not easy. Hippocrates in 400 BC wrote, about medicine in general, an aphorism that illustrates this difficulty: Life is short, the art long; the occasion fleeting; experience fallacious and judgment difficult. Medical decision making on ceasing systemic chemotherapy remains a very complex, intimate and subjective process. There are few and conflicting scientific data to guide treatments in this delicate setting.

the available data

What data do we have that characterizes the situation? Most of available data are retrospective death-centered studies, population or institution based [1]. The institution-based studies have access to the complete medical records where eventually data can be retrieved regarding decisions and goals of interventions. On the other hand, population-based studies, such as the one by Näppä et al. [2], and the Medicare system-based studies claim to picture reality in a more unbiased way.

In the current issue, Näppä et al. [2] examine chemotherapy administration in the last month of life. They have chosen a population-based cohort from Northern Sweden in which they were able to characterize 374 adults affected by solid tumors that were treated with chemotherapy in the last month of life. Their results show that one-fourth of Swedish terminal cancer patients still receive chemotherapy, which is in agreement with reports from other geographies. In this study, patients that receive chemotherapy have a shorter duration of metastatic disease, more hospital admissions and often lack a documented decision to stop chemotherapy.

Regarding other similar reports, two studies based on Medicare claims, encompassing roughly 8000 patients each, reported that 15% of terminal cancer patients receive chemotherapy in their last 2 weeks of life [3, 4]. In an institutional report from England, only 8% of the patients received chemotherapy in the last month of life but 7.5% and 4.3% of these patients had a toxic death or died of neutropenic sepsis, respectively [5]. Two institution-based studies from Italy showed that 23% and 15% of advanced cancer patients are receiving chemotherapy in the last month of life [6, 7]. Two similar Portuguese studies showed 37% and 13% of the patients being treated with chemotherapy in the last month of life [8, 9]. Further examples include two Korean reports, one where 30% of the patients receive chemotherapy in the last month of life and another where 50% receive treatment in the last 2 months of life [7, 10], and an Australian publication showing that 18% of cancer patients are being treated in the last month of life [11].

In these studies, the parameters presented as being predictors of receiving chemotherapy were young age, short metastatic
specifically affecting the ability to walk. The goals of palliative outpatients with good performance status, except in untreated Her2-positive disease [14].

In summary, up to a fifth of cancer patients are treated with chemotherapy in the last month of life without clear benefits (e.g. no prolongation of life) and sometimes even with visible negative consequences (increased toxicity, costs and decreased quality of life). The need to critically evaluate chemotherapy prescription in this context evokes four questions discussed below.

**will the patient benefit?**
Can doctors estimate patient survival in an accurate way? Most likely no; all physicians, oncologists in particular, tend to overestimate survival due to multiple reasons: strong emotional bonding, underestimating catastrophic complications and relative or forced stability during the doctor visit. A strategy to overcome this is to make frequent reassessments and ask experienced colleagues who have been shown to make more accurate predictions. It may also be beneficial to use evaluators like the Karnofsky performance score, the World Health Organization performance status, specific palliative scores or the assessment of specific symptoms. In the case of symptoms, the most informative are anorexia, weight loss, xerostomia, dysphagia and dyspnea. Among other validated variables are blood biochemical tests (e.g. low albumin, high lactate dehydrogenase, high interleukin-6) and cell counts (e.g. high white blood cell counts, low lymphocyte counts) [13]. Several attempts have been made to use algorithms for death prediction in terminal cancer patients but these have not met with general acceptance because of inefficacy, difficult implementation and ultimately because in terminal care the patient is viewed globally and thus such scoring systems are viewed as an oversimplification.

Is it appropriate to start or to continue chemotherapy? What are the symptoms? Are they cancer or toxicity related? If the main problems are pain, asthenia and cachexia, chemotherapy may not be the only and sometimes not even the most appropriate solution for them since it may exacerbate them. Performance status; asthenia; weight loss; marrow, cardiac and lung reserve as well as kidney and liver function help guiding the evaluation of the relative risks and benefits of using chemotherapy. If chemotherapy is agreed upon, this decision should be reevaluated frequently. The careful weighing of clinical benefits and risks is the core of this issue: *Primum non nocere*. In the majority of solid tumors of adults, a classic rule still stands that after three failed lines of chemotherapy the possibility of benefit with a fourth line is minute. However, there are exceptions, for example, in breast cancer, especially Her2-positive disease [14].

In short, chemotherapy should be limited to ambulatory outpatients with good performance status, except in untreated chemosensitive solid tumors or malignancies that are specifically affecting the ability to walk. The goals of palliative chemotherapy differ from those of curative chemotherapy because metastatic solid tumors are generally incurable; the aim is to increase survival. Furthermore, instead of focusing on lesion diameter shrinkage, a clinical trial end point, clinically relevant outcome measures like symptoms are possibly more adequate.

**what does the patient want?**
There are important cultural and religious variations in the acceptance of death. Data show that patients with high levels of positive religious coping tend to receive intensive life-prolonging care possibly because they believe in miracles and divine interventions [15]. However, if a religious counselor is provided from within the oncology staff, it reduces aggressive end-of-life care and increases hospice use [16]. Does the acceptance of death mean that all hope is lost? Hope is an important defensive mechanism. Somewhat paradoxically, there are data showing that giving honest information, even bad, maintains hope [17]. Some patients want to live a specific event before feeling prepared to die. If not possible, patients can find other ways to get a sense of purpose out of the event, such as writing a letter or recording a legacy. Many patients and families get great satisfaction from this.

There are tools and checklists for communicating bad news. During consultation, one can follow the stepwise approach of the SPIKES acronym: choose a setting (i), assess perception of the disease (ii), invite the patient to hear (iii), transmit knowledge (iv), assess emotional reaction with empathy (v) and summarize the care plan (vi) [18]. Why is not communication more effective? It is not because patients and families cannot bear to be informed on prognosis, it is because oncologists are insufficiently trained and, even for experienced physicians, giving bad news is just too hard. A simulated consultation study reported that poor performance was correlated with emotional burnout and fatigue but not inexperience [19]. In a study that recorded hematological oncology consultations in tertiary centers, care was not discussed quantitatively or at all in half of them [20]. A prospective study on palliative chemotherapy versus watchful waiting in advanced cancer patients showed that only 39% of patients reported discussing prognosis with the attending oncologist. In a longitudinal study, in admitted terminally ill cancer patients, 39% of the patients and 62% of the families said that the possibility of death had not been discussed [21]. Research shows that patients know more about their disease and their treatments at the time of diagnosis than at the time of relapse, progression and near death. One of the reasons for this discrepancy is that the established closer proximity between doctor and patient interferences with the physicians’ capacity to communicate unpleasant news [22]. Data show that when information is given to patients, it is provided with a range of values and patients cope with it by hoping to belong to the favorable tail of the distribution [21].

Information pays off. If physicians have discussed care at the end of life with their patients, patients are more likely to receive care according to their needs and preferences [23]. Additionally, when informed about their terminal illness, patients more often choose symptom-directed care [23].
Regarding biased or lack of information, a randomized trial of the use of the decision aid Adjuvant! for adjuvant breast cancer chemotherapy prescription concluded that only 58% (35 of 60) of the women who used the tool chose chemotherapy, while 87% (33 of 38) of the women that were informed by physicians chose it [24]. This is an indication that patients have unrealistically optimistic expectations on the benefits of chemotherapy.

In summary, fully understanding terminal patients’ wishes and goals, realistically addressing the potential and limitations of palliative chemotherapy and discussing end-of-life logistics are items of successful communication that might help spare useless treatments.

**can the patient get better care?**

It is harder to provide a good death than to cure a patient. Research has shown that terminal patients want to die at home, with loved ones, with symptom control, feeling independent and as conscious as possible [25]. For most cancer patients, this is difficult but achievable with the aid of specific skills that unfortunately are not widespread. For example, in a survey to second-year oncology fellows, only 23% carried out correctly an opioid conversion [26]. Cancer death is predictable, i.e. bedridden, pain, dyspnea, cachexia, anorexia, constipation, dehydration, fleeting consciousness and coma; therefore, it is easy to prepare families for it. After death, there might be an urge to move on, but, families in bereavement need follow-up, provide feedback and studies show it to be insufficient [27].

In the last decade, there was an expansion of palliative care units with doctors, nurses and supportive staff, dedicated full time to the terminally ill, that have shifted gear from a cancer-centric approach to a patient-centered approach. Palliative care should be gradually integrated so that the patient, family and medical oncology team do not feel as they are getting rid of the patient to die under the care of another team, away from the environment they lived in during the most extensive and easier part of the disease. The intervention of a palliative care team should start at the time of distant dissemination because the majority of metastatic patients are incurable. As the disease progresses, the emphasis slowly shifts from one of aggressive antitumor treatment to more focus on palliation. Near death, the only treatment is palliation with no blood tests, artificial feeding, emergency room or intensive care unit admissions.

In the last decade, there was an expansion of palliative care units with doctors, nurses and supportive staff, dedicated full time to the terminally ill, that have shifted gear from a cancer-centric approach to a patient-centered approach. Palliative care should be gradually integrated so that the patient, family and medical oncology team do not feel as they are getting rid of the patient to die under the care of another team, away from the environment they lived in during the most extensive and easier part of the disease. The intervention of a palliative care team should start at the time of distant dissemination because the majority of metastatic patients are incurable. As the disease progresses, the emphasis slowly shifts from one of aggressive antitumor treatment to more focus on palliation. Near death, the only treatment is palliation with no blood tests, artificial feeding, emergency room or intensive care unit admissions because families communicate by phone with the staff that visits at home. Why, then, are patients and families sometimes reluctant to accept this? Apparently due to lack of information. Studies have shown higher use of hospice care by informed patients [21]. Additionally, palliative care should not be a oneway road. Different reimbursement systems in some countries might preclude the utilization of hospice care because patients transferred to hospice lose the rights to cancer center care. It would be an improvement if in this setting patients gained rights instead of loosing rights.

Is chemotherapy more effective than best supportive care as treatment of metastatic cancer? This depends on how one defines ‘effective’. If it is survival, then, yes, chemotherapy prolongs survival in the majority of metastatic solid tumors of adults. So the question is not if it should be administered but rather until when should it be administered. On the other hand, if effective means achieving a ‘good death’, with symptom control and quality of life, chemotherapy is not as good. But, do hospice patients die sooner? A retrospective study designed to answer this question actually found either prolongation of life, in case of lung cancer, or no difference, in case of three other common solid tumors (breast, colon and prostate carcinomas). This study is based on Medicare records and the inclusion criteria for the hospice care group is one Medicare claim. Therefore, it might reflect better care in general and not necessarily capture the dichotomy between chemotherapy administration and symptom control [28].

Finally, research must be conducted regarding end-of-life care to identify which patients are best managed with etiological versus symptomatic approach. Qualitative outcomes and health services research increased through the 90s and peaked in 2000 [29]. Futility, toxicity and aggressiveness are measured by following patients with a predicted reduced life span prospectively and collecting data on the justifications, decisions and goals of terminal care interventions and recording indicators of aggressiveness, like emergency room, intensive care unit admissions and surgeries.

**are there conflicts?**

Oncologists are frequently subject to pressure sometimes from patients but more often from families to continue therapies of doubtful efficacy [30]. Conflict often starts with members of the family that are absent or health illiterate [31].

There are health care systems in which the physician and the institution are better reimbursed for chemotherapy administration and by requesting radiological examinations than for carrying out a complex cognitive discussion. In fact, there are systems where burdensome family conferences are not reimbursed. This creates a perverse incentive because the hardest actions are poorly compensated, while the easier ones are more lucrative. This would be avoided if reimbursement was done on the basis of consultation with the physician with no link to drug administration. Additionally, admitting that there are better alternatives for symptom control and quality of life preservation might include the referral to another team of physicians and the potential loss of the patient as client of the clinic.

Lastly, why is not there more research on terminal cancer care, as has been discussed? Clinical cancer research mainly asks drug-oriented questions by doing clinical trials. But even academic trials led by institutions and collaborative groups are exquisitely dependent on pharmaceutical industry funding to happen. It is extremely difficult to fund applied clinical research questions that do not involve drugs; this might be one of the reasons it is less attractive.

**the patient, again**

At this point, I return to the initial story and imagine how I could have done better. Regarding the first question, I should have assumed that widely metastatic alveolar rhabdomyosarcoma was likely to be chemoresistant. The specific disease had taken an aggressive biological behavior, the
lesion was increasing daily and the natural history of the untreated primary had only 4 months. I should have set my goals accordingly. The patient, who was supposedly a fit young woman, had feebly marrow reserve, possibly because of infiltration, which I should have diagnosed. Her performance status was three, i.e. she was partially bedridden, with lung metastases, so the potential for infectious complications, with the regimens used, was high. Her symptoms were pain in the primary lesion, which was well controlled with morphine, and she was not dyspneic.

Regarding the three other questions: What did she want? She wanted to be with her baby daughter, husband and parents, at home. Was there a better team to care for her? Possibly, yes. I do not think that she would have objected to a discussion about therapeutic futility and end-of-life care by different staff, provided the medical oncology team could remain available.

Were there conflicts? Not at all. They had accepted distressingly peacefully the catastrophe of incurable cancer at a young age.

What went wrong? Why did this young woman get chemotherapy until the end of life? Clearly because I failed. I hope I have learned the lesson.

funding

The Programme for Advanced Medical Education is sponsored by Fundação Calouste Gulbenkian, Fundação Champalimaud, Ministério da Saúde e Fundação para a Ciência e Tecnologia, Portugal.

S. Braga*
Instituto Português de Oncologia and Instituto Gulbenkian de Ciência (Gulbenkian Program for Advanced Medical Education), Lisbon, Portugal

(*E-mail: sbraga@igc.gulbenkian.pt)

disclosure

The author declares no conflict of interest.

references