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REVIEW ARTICLE

Management of the toxicity of chemotherapy and targeted therapies in elderly cancer patients

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Abstract
The elderly form a very heterogeneous group in relation to their general health state, degree of dependence, comorbidities, performance status, physical reserve and geriatric situation, so cancer treatment in the older patient remains a therapeutic challenge. The physiological changes associated with aging increase the risk of developing a serious toxicity induced by chemotherapy treatment, as well as other undesirable consequences as hospitalizations, dependence and non-compliance with treatment, that can negatively affect survival, quality of life and treatment efficacy. The use of hematopoietic growth factors and other active supportive interventions in the elderly can help prevent and/or alleviate these toxicities. However, we have little data on the efficacy and tolerance of support treatments in the older patient. The objective of this work is to review the most frequent toxicities of oncological treatments in the elderly and their management.

Keywords Cancer · Elderly · Chemotherapy · Toxicity · Support treatments

Introduction

During the last decades there have been very important advances in the pharmacological treatment of cancer, with the incorporation of new chemotherapeutic agents and the irruption of targeted therapies and immunotherapy. However, the experience with these drugs in the geriatric population is still scarce and, as a consequence, side effects are often overestimated and their potential benefits are underestimated, resulting in a decreased frequency of prescription in this group of patients [1].

Cancer treatment in the older patient continues to represent a therapeutic challenge for different reasons: (1) elderly patients form a very heterogeneous group in relation to their health condition, degree of dependence, comorbidities, performance status, physical reserve and geriatric situation, which hinders therapeutic decisions; (2) with aging, physiological changes can modify the pharmacokinetics and pharmacodynamics of the drugs as well as the tolerance of the tissues, leading to a narrowing of the therapeutic margin and an increased toxicity; (3) in the elderly, comorbidities and polypharmacy are frequent, which favor the risk of drug interactions and contributes to increasing the risk of suffering toxicities with the treatment; (4) there are few studies on the prevention and management of the toxicity of antineoplastic treatments specifically performed in older patients; (5) There are few data on the efficacy and toxicity of antineoplastic treatments in real life. In fact, the main data available are from clinical trials, but these patients are selected, with an excellent health condition and no comorbidities, so they are hardly representative of what really happens in the global geriatric population [2].

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The objective of this work is to review the most frequent toxicities of oncological treatments in the older patient and their management.

Does the toxicity of antineoplastic treatments increase in the elderly?

It is usually considered that chemotherapy is associated with an increased risk of toxicity in older patients, of which about 30–50% will experience a severe episode (grade 3–5) [3–6]. These variations depend on the type of chemotherapy administered and the individual characteristics of the patient [1].

When interpreting the clinical value of these data, it should be considered that in most cases hematologic toxicity refers to laboratory parameters and has little clinical significance. On the contrary, non-hematologic toxicity has a much greater impact on the quality of life of the patient. Besides, the impact that these toxicities can have on functional capacity, emotional sphere, cognitive function and on the use of health resources is unknown [7]. A particularly undesirable consequence of the toxicity of chemotherapy in the elderly is hospitalization, since it often causes an irreversible decline in functional capacity, loss of independence and an increased risk of institutionalization [8, 9].

In addition to the problem of acute toxicity, the repercussions that delayed toxicity may have on the elderly should also be considered [10]. It has been described that cardiotoxicity frequently occurs (especially in patients with previous heart disease), neurological toxicity [11], cognitive deterioration, metabolic syndrome, worsening of diabetes and reduced mobility and independence.

In recent years, numerous targeted therapies have been incorporated into the therapeutic arsenal. Their toxicity is much more bearable than that of chemotherapy and, in general, rarely poses a threat to life [12]. However, the use of these therapies in the elderly raises doubts about their therapeutic compliance and the risk of interaction with the usual polypharmacy that this age group usually takes. Moreover, grade 2 toxicity may be bearable for a few weeks, but it can have devastating consequences on the quality of life if it is maintained over time [13].

Evaluating the risk of developing toxicity induced by treatment

The elderly are a very heterogeneous population with high risk of suffering severe toxicities during antineoplastic treatment. The consequences of this toxicity in the elderly are especially serious, since they can suppose a decrease in the quality of life, lead to a dependency situation and, even, put their lives at risk. Besides, with aging the frequency of comorbidity and polypharmacy increases and therefore the risk of drug interactions. In addition, metabolism and elimination of antineoplastics can be modified. Several studies have related polypharmacy with an increased toxicity of chemotherapy in the elderly. Hence, it is always necessary to review the concurrent medication by comorbid processes, to avoid interactions [14].

Therefore, it is crucial to have tools that help us predict the risk of suffering a severe toxicity during an antineoplastic treatment to individualize the treatment and adopt the appropriate preventive measures. One of the tools with most clinical evidence is the comprehensive geriatric assessment (CGA) (Table 1), that allows the recognition of health problems and the detection of vulnerability states. In addition, it helps to estimate the risks of complications, hospitalization or death due to treatments, which can help in therapeutic decision making [15–17]. In the specific case of chemotherapy, the CGA allows the identification of some groups of patients: (1) fit patients, who can receive the same treatment as those of other age groups; (2) fragile patients that give their comorbidities and poor functional status, it is doubtful that they will benefit from chemotherapy. In these patients the treatment should rather be oriented towards palliation; (3) vulnerable patients, who need preventive and proactive measures. In these cases, a tailored geriatric intervention should be performed to improve the impaired GA domains. After its application, the patient should be re-evaluated to see if the situation has been reversed and, therefore, chemotherapy can be administered. In these scenarios, dose reductions or monotherapy treatments can be considered.

In spite of its advantages, the performance of a CGA has not yet been generalized since its realization is time-consuming and there is a shortage of trained clinical personnel to carry it out [18]. Also, in some patients it may not be necessary to perform it. Therefore, screening tools such as G8 and VES13 have been developed to identify which patients will benefit from completing a full CGA [19, 20]. G8 has a strong predictive value for nutritional status and VES 13 has a stronger predictive value for impairment of functional status (ADL and IADL). In those cases in which their values exceed the established limits, a CGA should be carried out.

On the other hand, specific tools have been developed to help distinguish between older adults with low or high risk of suffering chemotherapy-derived toxicity [21–26]. In some cases they were designed in patients with a certain type of tumor [24–26], so their results cannot be extrapolated to other neoplasms, in other cases they have not been validated externally [22, 23] and in others, despite them being validated [27], it has not been possible to confirm their utility in some series [28]. Also, in the best scenario, in up to 30% of the cases the prediction is incorrect, so we should be prepared to handle the toxicities that may appear.

Table 1 Geriatrics tools included in the CGA

Variable	Tool
Demographics and social status	Age, sex, general situation at home, marital status, educational level, economic resources MOS Social Support Scale
Comorbidities	Charlson Comorbidity Index (CCI) NYHA Functional Classification Cumulative Illness Rating Scale-Geriatrics (CIRS-G)
Functional status	Performance status ADLs IADLs MOS physical health Short Physical Performance Battery (SPPB) 4-Meter gait speed test Chair stand test Balance tests (side-by-side stand, semi-tandem stand) Vulnerable Elders Survey (VES-13)
Cognitive status	Mini mental Pfeiffer scale Concentration test
Psychological (anxiety and depression) and social	HADS score Mental health index Associated depressive syndrome Simplified MOS Scale Gijon's social-familial evaluation scale (SFES)
Nutrition	Body mass index (BMI) Weight loss in recent months
Geriatric syndromes	Dementia, delirium, urinary or fecal incontinence, osteoporosis, spontaneous fractures, abuse, falls in recent months, constipation, polypharmacy, pressure ulcers, sarcopenia, etc
Oncological variables	Variables related to the primary tumor, stage and treatment scheme, dose, laboratory parameters (HB, LDH, etc.)

Treatment-related complications and their management

Hematologic toxicity

With aging the hematopoietic stem cell reserve decreases and the risk of myelosuppression associated with chemotherapy increases [29]. Myelotoxicity is the dose-limiting toxicity of many cytostatic agents and, in particular, of alkylating agents. Many of the toxicities are caused by the metabolites rather than by the drugs themselves. Therefore, changes in metabolism associated with age will increase the risk of toxicity [30]. Table 2 shows the hematologic toxicity and its management.

Neutropenia

Neutropenia is the main dose-limiting toxicity. Neutropenic fever is a serious complication of chemotherapy. Its appearance involves delays in the administration of treatment and dose reductions. It can compromise the efficacy of chemotherapy and favor the development of severe and potentially lethal infections, especially in patients with previous

Table 2 Hematologic toxicity of oncological treatments in older patients and its management

Toxicity	Possible prevention/treatment	Risk or limitations in the elderly
Neutropenia	Prophylactic use of granulocyte colony-stimulating factor (G-CSF) Dose reduction Levofloxacin	Indicated if the risk of febrile neutropenia is ≥ 10%. Less effective in the elderly Prolongation of QTc interval
Anemia	Erythropoiesis-stimulating agents (cytotoxic chemotherapy only) Blood transfusions	↑ Risk of thromboembolic event if age ≥ 75 years or comorbidities
Thrombocytopenia	Platelet transfusions	

comorbidities [31]. The clinical guidelines recommend the use of colony-stimulating factors (G-CSF) in the elderly candidate for myelosuppressive treatment since they have shown to be effective in reducing the degree and duration of leukocyte nadir [32, 33].

The points to consider for their indication are: the risk of developing febrile neutropenia due to the chemotherapy scheme administered, the patient's characteristics (such as previous episodes of neutropenia), the comorbidities and the intention of the treatment [32, 34, 35]. The guidelines state that primary prophylaxis should be administered when the therapeutic schemes used carry a risk of developing febrile neutropenia ≥ 20%. However, its administration should also be evaluated in patients over 65 years with a risk of 10–20%, especially if they have other comorbidities [36]. In any case, the risk of neutropenia assessment usually comes from trials conducted in the adult population, not specifically in the elderly [34]. In fact, despite its use, 16.6% of the elderly population continue to experience neutropenic fever [32], which suggests that the recommendations are not fully refined. There is an important clinical need to identify the characteristics that make this population more vulnerable to hematological toxicity. In this sense, it has been recently reported that prophylaxis with G-CSF obtains worse results in the elderly [37]. In another study it was observed that the elderly with more than two comorbidities were at a higher risk of developing fever despite receiving prophylactic treatment with G-CSF [32].

Some studies support the use of prophylactic antibiotics in patients with solid neoplasms and lymphomas [34]. In a randomized double-blind trial, patients who received prophylactic levofloxacin experienced less febrile neutropenia than those who did not (10.8% vs. 15.2%, $p < 0.001$) [38]. However, in this work, elderly patients were underrepresented. In addition, they present a greater risk of toxicity associated with the use of quinolones (prolongation of the QTc interval), which may limit their use in this population.

Anemia

It is common for the older patient with cancer to have anemia, but this problem can be aggravated as a consequence of the treatment. Anemia conditions the reduction of the distribution volume of the drugs, increasing their maximum concentration and toxicity. In severe degrees, anemia produces asthenia, which can cause functional deterioration, physical and mental fatigue. Anemia can also unbalance previous comorbidities, such as cardiovascular and dementia [39].

For the treatment of anemia in patients with non-hematologic cancer secondary to chemotherapy, and depending on the degree of severity and clinical circumstances, the transfusion of concentrated red blood cells and/or erythropoietin (EPO) is used [40–42]. The administration of EPO is not recommended in patients with anemia and cancer outside the period of administration of chemotherapy. The administration of EPO has been related to an increased risk of thromboembolic events (TEE), as well as an increased risk of hypertension and headache [40]. However, when the treatment is aimed at raising the hemoglobin level to 12 g/dl, EPO-induced TEE should rarely be a problem [43].

In a recent study it was reported that patients over 75 years and those with a Charlson index greater than 0 were more likely to suffer hospitalization for a TEE [44]. Studies show contradictory data, but it seems that its administration in patients with cancer increases mortality [45, 46], so it is not recommended in patients with treatments with curative intent, except in small cell lung cancer [40].

Thrombocytopenia

Thrombocytopenia is a dose-limiting effect. It currently has no treatment except for the transfusion of platelets in certain indications. Therefore, it conditions the modification and/or interruption of treatment. Clinical trials are ongoing for patients with thrombocytopenia secondary to chemotherapy with thrombopoietin-stimulating agents such as romiplostim and eltrombopag.

Non-hematologic toxicity

Nausea and vomiting

Nausea and vomiting induced by chemotherapy are side effects that can significantly affect quality of life and treatment compliance. Older patients are less likely to suffer them, but they present an increased risk to develop toxicity associated with antiemetic drugs, since antagonists of the 5-HT3 receptor can prolong the QTc interval of the electrocardiogram and generate arrhythmias, so they should be used with caution in patients with cardiovascular comorbidity. Likewise, complications due to the use of exogenous corticosteroids, such as hyperglycemia, especially in diabetic patients, should be avoided, or the interactions of the neurokinin-1 receptor antagonist, aprepitant, with other drugs, as it is a moderate inhibitor of cytochrome P-450 isoenzyme 3A4 (CYP3A4) [47]. In addition, it should be remembered that the elderly are more susceptible to neurological toxicity of neuroleptics, such as metoclopramide, and may have extrapyramidal effects. All this leads to individualize the selection of antiemetic therapy in the elderly according to their characteristics (Table 3).

Diarrhea

With aging stem cells decrease and the intestinal mucosa atrophies, and this may favor the appearance of diarrhea.

Table 3 Selected non hematologic complications of oncological treatments in older patients and their management

Toxicity	Possible prevention/treatment	Risk or limitations in the elderly
Nausea/vomiting	Antagonist of the serotonin 5-HT3 receptor	Prolongation of QTc interval
	NK1 receptor antagonist	Interaction with CYP3A4
	Metoclopramide	Extrapyramidal effects, hyperglycemia. Use the lowest possible doses, and for short-term
	Corticosteroids	
Diarrhea	Loperamide	Hyperglycemia. Use for short-term
	Octreotide for severe/resistant cases	
	IV Hydration	
	Corticosteroids for check-point inhibitors	
Mucositis	Oral hygiene	Scarce experience in the elderly
	Benzydamine mouthwash	
	Management of mucosal infections	
	Low-level laser therapy	
	Palifermin	
Cardiac toxicity	Cardiac monitoring	↑ Risk if previous cardiopathy
	For anthracyclines, dexrazoxane	
Neurological toxicity	↓ Drug dose	Drowsiness and confusion
	Gabapentine/pregabaline	
	Duloxetine	
Osteoporosis	Calcium and vitamin D	Not indicated in case of renal insufficiency
	Bisphosphonates	
	Denosumab	
Asthenia	Methylphenidate	Insomnia, anxiety, agitation, dyskinesia, arrhythmia, arterial hypertension
	Steroids	Hyperglycemia. Use the lowest possible doses, and for short-term
	Panax quinquefolins	Insomnia, hypoglycemia

It is a common side effect with certain types of cytostatics such as 5-fluorouracil (5-FU), capecitabine and irinotecan, and also with some targeted therapies such as tyrosine kinase inhibitors (TKI). In the population ≥ 70 years, there is an increased risk of grade 3–4 diarrhea when treated with irinotecan [29]. In the elderly, a closer monitoring is recommended to prematurely detect the development of toxicities.

The main risk of diarrhea is the loss of electrolytes and fluids and conditions dehydration, renal failure and electrolyte imbalance. Chemotherapy-induced diarrhea results in dose reductions, delays or even discontinuation of treatment. The ASCO guidelines recommend loperamide as a treatment [48] (Table 2). When oral antidiarrheals are ineffective, treatment with octreotide is recommended [49]. In addition, administration of *Lactobacillus* may be useful [50].

Immunotherapy with PDL-1 or CTLA4 inhibitor drugs such as ipilimumab, nivolumab or pembrolizumab can also induce diarrhea of autoimmune origin. In these cases, the treatment usually consists of the administration of corticoids.

Mucositis

The risk of mucositis increases with age. Severe mucositis can cause dysphagia, malnutrition and dehydration, which could be lethal in elderly patients. The main chemotherapeutic agents that produce it are 5-FU, methotrexate and doxorubicin.

To prevent the development of chemotherapy-induced mucositis extreme oral hygiene is recommended. Cryotherapy for 30 min may be useful in patients receiving 5-FU administered in bolus. However, it has not been possible to establish the efficacy and safety of the use of topical antibiotics, sucralfate, anti-inflammatories, glutamine, antioxidants, etc. [50, 51]. The treatment of mucositis includes adequate hydration and analgesics and in severe cases it may require hospital admission for rehydration and nutrition. The only drug approved for treatment is palifermin, but the trial that established its indication only included patients aged ≤ 70 years [52] and there are no specific studies in the elderly population (Table 2).

Cardiac and vascular toxicity

The risk of cardiovascular toxicity is estimated to double for every 10-year age increase [53]. The main risk factor in the elderly population is the previous presence of cardiovascular comorbidity, especially if they have arterial hypertension, heart failure, diabetes mellitus, coronary disease, etc., and also if they have previously received anthracyclines. These drugs can induce cardiotoxicity, even at low doses, in a population with pre-existing lesions [10, 54]. To prevent anthracycline cardiotoxicity, the use liposomal formulations has been proposed as well as the prolongation of the infusion time and the use

of cardioprotective drugs such as dexrazoxane. However, when the treatment has a curative intention, it is essential that the measures adopted to avoid cardiotoxicity do not compromise the efficacy of the treatment [55].

In the case of trastuzumab, although it has been pointed out that age represents a risk factor for developing congestive heart failure, it seems that this risk depends more on the preexistence of comorbidities than on age itself [56]. Likewise, the administration of TKI angiogenesis inhibitors has been related to a higher incidence of heart failure and is a cause of great concern in the elderly population, which often has cardiac comorbidity [55–57].

Another population that also presents an increased risk of cardiovascular toxicity is men with prostate neoplasms treated with an androgen blockade. For each year of increase in age, the risk of cardiotoxicity increases by 3% [10].

The administration of 5-FU and its derivatives in the older patient is associated with an increased risk of cardiac toxicity. Its incidence varies from 1.2 to 18% and usually manifests during treatment with chemotherapy. With capecitabine, ischemic cardiac disease has been described in up to 9% of patients.

When vascular endothelial growth factor receptor inhibitors (angiogenesis inhibitors) are used, age is an important risk factor for the development of thrombosis and hypertension. A pooled analysis of five randomized trials of patients with various metastatic cancer types, treated with bevacizumab, demonstrated that age over 65 years is an independent risk factor for presenting arterial thromboembolic events, particularly if bevacizumab is administered in combination with chemotherapy [58]. This risk is even greater if, together with age, there is a history of arterial thrombotic events [59].

Renal toxicity

It is common for elderly patients to have a previous deterioration in renal function that can worsen with the use of nephrotoxic drugs. Serum creatinine is not a good indicator of renal function in the elderly population and the calculation of creatinine clearance is recommended to make dose adjustments. To prevent the deterioration of renal function during treatment, it is important to adequately hydrate the patient and avoid toxicities that put water intake at risk or facilitate losses, such as nausea and vomiting, mucositis or diarrhea.

A recent study revealed that for every 10 mL/min decrease in creatinine clearance the odds of chemotherapy-related toxicity increased by 12%, independently of the type of chemotherapy received [60].

Neurological toxicity

Neurotoxicity is the dose-limiting toxicity of certain cytostatics. Older patients are particularly susceptible to neurotoxicity, especially if they have some previous neurological pathology, such as diabetic neuropathy.

Platinum-derived agents and anti-microtubule agents (paclitaxel, docetaxel, vincristine, vinorelbine…) produce peripheral neurological toxicity. In the elderly, the effect of age on the toxicity of these drugs is uneven. While with paclitaxel the incidence of symptomatic peripheral neuropathy significantly increases in elderly women with ovarian cancer, there is no evidence of an increase in the risk of neurotoxicity caused by oxaliplatin [61].

Patients over 60 years are particularly susceptible to the cerebellar toxicity of cytarabine. Factors that influence the development of this complication are the administration scheme, the dose and the presence of renal or hepatic dysfunction [62]. Methotrexate and ifosfamide induce central neurological toxicity and purine analogs (fludarabine, cladribine, pentostatin) cause lethal neurotoxicity at high doses.

Chemotherapy-induced peripheral neuropathy in the elderly is associated with falls and functional impairment that increase when using schemes with two neurotoxic drugs instead of one [63], and in those patients who have some prior dependence for routine activities [64, 65].

The management of neurotoxicity mainly consists of reducing the doses of the responsible drugs. Neuropathic pain may respond to the administration of duloxetine [66]. Likewise, it may respond to high doses of gabapentin or pregabalin, although these drugs may cause drowsiness and confusion in the elderly [67] (Table 2).

Ototoxicity

Ototoxicity can occur in the form of tinnitus or bilateral hearing loss. Cisplatin generates ototoxicity around 19–79% in the adult population. In the elderly, ototoxicity can increase the risk of falls, accelerate cognitive deterioration and worsen the quality of life [68].

Effects on bone health

Osteoporosis and the risk of fractures increase with age and cancer treatments [69]. It is estimated that patients receiving antineoplastic treatments have a 5.1 times higher risk of developing osteoporosis than that of the general population. Specifically, while tamoxifen decreases the risk of osteoporosis, aromatase inhibitors in breast cancer, and androgen deprivation in the prostate, increase it. For example, in a study conducted on patients diagnosed

with prostate cancer under hormonal treatment, 19.4% of patients suffered fractures during a 5-year follow-up period [70]. Despite this high risk of osteoporosis and fracture, up to 77% of cancer survivors with osteoporosis are not diagnosed by primary care [71].

To avoid the development of bone events, the state of bone density should be evaluated at the beginning of the treatment. If it is normal it should be maintained by the administration of calcium and vitamin D supplements [72]. In addition, changes in lifestyles, physical exercise, quitting smoking and avoiding alcohol consumption are recommended. If osteopenia or osteoporosis is detected, administration of bisphosphonates or denosumab may be necessary. In patients with bone metastases these drugs increase bone mineral density and reduce the number of related bone events. It should be taken into account that bisphosphonates are not indicated in patients with poor renal function (Table 2).

Fatigue

Asthenia is a symptom related to cancer and its treatment. In addition, it represents one of the most frequent long-term sequelae after cancer treatment. Asthenia negatively impacts quality of life, causes functional dependence and reduces social activities. Its origin is usually multifactorial: antineoplastic treatment, anemia, malnutrition, anxiety and depression, sleep disturbances, concomitant medications, etc. Its prevalence and incidence increase with age, polypharmacy and sleep disorders.

To prevent it, it is necessary to lead an active life, with daily physical exercise during treatment, as well as having adequate nutritional support, maintaining hemoglobin levels ≥ 12 mg/dL and depression management, beginning at the same time that oncological treatment [73, 74]. Regarding pharmacological treatments, the heterogeneity of patients with asthenia related to cancer and the complexity of the design of rigorous studies prevents conclusions from being drawn. Of all of them, those that seem to have more solid results are those that were performed with psychostimulants and dexamethasone [75]. However, it is important to remember the long-term toxicity of corticosteroids and especially their effects on muscle catabolism and glucose metabolism, which restrict their use to the palliative context [76]. Another treatment that may be effective in relieving asthenia is the administration of American ginseng (*Panax quinquefolins*). In a phase III trial, it was reported that after 8 weeks of treatment, patients had significantly less asthenia than the placebo group [77]. On the contrary, in another recent study, the administration of Asian ginseng (*Panax ginseng*) did not manage to improve this symptom [78].

Dermatological toxicity

Targeted therapies often induce skin toxicity, mainly acneiform rash and hand-foot syndrome. Growth factor receptor inhibitors such as erlotinib, gefitinib, cetuximab or panitumumab can cause skin rash and acneiform reactions. It does not seem that the cutaneous toxicity of these drugs increases with age [13, 79], although in the case of erlotinib there are contradictory data [13]. The treatment consists of the application of a moisturizing ointment and topical corticosteroids, to which topical clindamycin gel can be added or oral antibiotics, such as doxycycline, in more severe cases.

The drugs that most frequently produce hand-foot syndrome are sunitinib, sorafenib and regorafenib [80], in addition to capecitabine and liposomal adriamycin. The treatment consists of applying topical creams with urea or salicylic acid, as well as corticosteroids and topical anesthetics if necessary. In the clinical practice, if the cutaneous toxicity reaches degrees over 2, it can lead to the temporary interruption of the treatment, with re-initiation sometimes at reduced doses, or even to its definitive interruption. Treatment interruption rates due to severe toxicity are 3%, but it is difficult to generalize this data since studies on this subject are very heterogeneous [81].

Finally, it should be noted that treatment with vemurafenib in patients aged ≥ 75 years has been associated with an increased incidence of squamous cell carcinoma of the skin (18% vs. 6%) and keratoacanthoma (10% vs. 6%) [82].

Other repercussions of toxicity

In addition to the toxicities that have been reviewed, antineoplastic treatments may have other undesirable consequences in the elderly, such as dependence, hospitalizations, reduction of drug doses, decrease in the number of cycles and suspension of antineoplastic therapy. All this can negatively affect survival, quality of life and treatment efficacy.

Quality of life, functional deterioration, and dependence

Treatment toxicity can aggravate preexisting geriatric syndromes, which can contribute to worsening an already precarious functional state and, even, cause death. Functional dependence is the consequence of a combination of factors including malnutrition, sarcopenia, asthenia and neurotoxicity. As a consequence of cancer treatment, older cancer survivors have an odd developing frailty of 1.46 (95% CI 1.29–1.65) compared to older persons without a history of cancer [83].

Therefore, it is necessary to identify the fragile patients to make therapeutic decisions and establish appropriate support

measures through the rehabilitation of functional dependency with specialized teams. It should be noted that when deciding whether to undergo an antineoplastic treatment, the elderly give as much importance to the potential benefit on survival as to its impact on the quality of life [84].

This vulnerable elderly population with metastatic cancer can benefit from the administration of adapted oncological active treatments, such as the use of monotherapy or metronomic chemotherapy, which can be effective in alleviating symptoms and has less impact on the quality of life [85, 86].

Hospitalization

An undesirable consequence of antineoplastic treatments in the elderly is the increase in hospital admissions. In a large prospective study conducted in a cohort of more than 2000 adult patients with diverse cancers who received chemotherapy, 8.7% of patients required hospitalization for the toxicity of the treatment, with almost 1% of deaths. There were no significant differences in the rate of admissions based on age, although the number of elderly patients included was relatively low [87]. It has been observed that two thirds of the admissions occur during the first cycles of chemotherapy and it is more frequent that they occur if the purpose of the therapy is curative or if it has an indication of adjuvant, as opposed to those administered with palliative intention [88].

Comorbidity is the factor that most influences the need for hospitalization in patients receiving chemotherapy. For this reason, caution should be taken with the prescription of chemotherapy to elderly patients who present multiple comorbid conditions.

Inadequate treatment compliance

Another repercussion of toxicity in older patients treated with oncological therapies is the lack of accomplishment and the voluntary cessation of the treatment, which may have a negative impact on the result.

We have little data on the rates of desertion of cancer treatment in the elderly. Advanced age per se is not a consistent risk factor for non-adherence to treatment, but elderly patients more frequently present various factors that do influence drop-out: the toxicity of the treatment [89, 90], the personal experience of the disease and treatment, perception of control, knowledge of the importance of adherence and the consequences of not adhering, knowledge of the disease and the treatment [91], cognitive deterioration, comorbidities, polypharmacy, limited insurance coverage and inadequate social support [92]. In addition, depression, anxiety and social isolation, prevalent conditions in the elderly population, are also related to low adherence.

In prolonged oncological treatments of chemotherapy and radiotherapy, adherence is lower, reaching a decrease in compliance of up to 20% [89]. Lack of adherence and/or interruption of adjuvant hormone therapy have been reported in 15–50% of women with breast cancer. Factors that influence this lack of compliance include age $\geq$ 75 years and the increase in the number of comorbidities 3 years after diagnosis [93]. The increase in mortality is the most important consequence of the lack of therapeutic compliance secondary to toxicity [94, 95].

The concept of adherence is directly related to the making of shared decisions and the patient's involvement in the follow-up of instructions and therapeutic prescriptions, but there are few research studies that support the effectiveness of psychological interventions to promote adherence to anticancer treatments.

Conclusions and future directions

Despite the high frequency with which cancer is diagnosed in the elderly, experience with antineoplastic drugs is scarce in this population, so their side effects are often feared and their potential benefits are underestimated.

The data available in the literature come from clinical trials, but the population included is usually very selected for its excellent state of health and does not represent the overall of the elderly population. Therefore, it is essential to have data on the efficacy and tolerance of treatments in real life, outside of clinical trials, where the population is less selected and the follow-up is not as strict. In this more heterogeneous population, the effectiveness of the treatments may be lower and the toxicity may be detected later and result more severe. On the other hand, clinical trials usually do not include information on the impact of treatment on important aspects in the geriatric population such as quality of life, functional capacity, need for hospitalization, etc. All this means that we do not know how the toxicity of antineoplastic treatments impacts on those components of health and quality of life that go beyond the classical measurement of toxicity collected by the NCI-CTCAE criteria. To acquire this information, it would be important for a CGA to be carried out on all the elderly patients who are going to initiate an antineoplastic treatment and to repeat it throughout the scheme, to evaluate the impact of the treatment on their health.

Many of the new treatments are administered chronically for long periods of time and, although they do not produce severe toxicities, they do induce moderate toxicities (grade 1–2) that are maintained for long periods. Again, we do not know the impact that these moderate, but long-lasting toxicities can have on the older patient. Likewise, we lack more studies on the possible repercussions that the sequelae of treatments may have on the quality of life and health of the elderly who survive a cancer.

To prevent the development of toxicity or to alleviate it when it has occurred, the same strategies apply as in the younger population, with the use of hematopoietic and other active supportive interventions. It is also convenient to perform a closer monitoring of the patients to detect its appearance and apply early support treatments. However, again, we are missing studies that inform us about the efficacy and tolerance of supportive treatment in the older patient. Given the foreseeable increase in the number of elderly patients with cancer, research and educational initiatives targeted to this population will be a priority.

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