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Current Perspective

Vulnerable and frail elderly: An approach to the management of the main tumour types

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ABSTRACT

In dealing with older cancer patients undergoing chemotherapy, some form of geriatric evaluation is needed to distinguish those which can be treated as adults from those – the vulnerable ones – who need a modified approach and also from those who are frail or too sick to receive an active treatment. Only scarce data are available to guide treatment of vulnerable or frail patients, the neglected majority of older cancer patients. In most of these cases they receive an adapted approach which does not derive from the results of clinical trials, but from an enlightened empiricism. In this article we summarise and discuss available data for management of the main tumour types in frail and vulnerable patients, and call for further research in this field.

1. Introduction

While planning a medical therapy for an older cancer patient, we are continually in the position of deciding whether this case should be treated with full dose chemotherapy or with reduced doses or, as a third option, without an active treatment if he or she is too sick to receive it. The Performance Status (PS) has been an useful instrument for adult patients to orient the therapeutic decision, but in the elderly, the Multidimensional Geriatric Assessment (MGA)[1–3] adds to the simple PS[4] since it covers the multifaceted features of age-associated conditions.

There is no doubt that a complete MGA will provide more information compared to PS on the capability of the old patient, for example, of phoning a physician or a nurse, using public transportation or taking medications.[5] More than the simple PS, assessment of Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) will give information on the degree of autonomy of the old patient. The possibility of being taken care of depends also on the mental status and presence or absence of depression, but PS again does not give any information on these parameters.

However, a full MGA is seldom carried out even by those Medical Oncologists interested in taking care of older pa-

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tients.[6] Most probably this is due to the considerable amount of time requested by an extended geriatric evaluation.[7] From a practical point of view, we believe that one should trust one of the available instruments[1–3,8–10] to distinguish those patients who can be treated as adults from those who need a modified approach and also from those who are too frail or sick to receive an active treatment. This distinction can therefore no longer be made 'at a glance' or by simply relying on the PS.

In this perspective an effort has been made to report data resulting from trials or from current clinical experience to deal with older patients needing a modified approach to chemotherapy in some of the most common tumour types.

2. Breast cancer (BC)

Vulnerable and frail women with BC are usually treated based on the physician's personal experience and are at high risk of not receiving standard care procedures on the assumption that BC is an indolent disease at this age.[11] The use of MGA has indeed been demonstrated to be able to uncover significant elements influencing the management of BC in a cohort of elderly women followed at the Senior Adult Clinic at Moffitt Cancer Center in Tampa.[12]

Adjuvant endocrine therapy with tamoxifen or aromatase inhibitors reduces the risk of relapse and controlateral tumours and is currently administered to almost all elderly patients with endocrine responsive disease, but concomitant comorbidity may strongly influence the choice of the endocrine agent.[13] Tamoxifen carries a risk of thromboembolism around 5% and should therefore be administered with caution in women with impaired physical functions or with previous thromboembolic events. Aromatase inhibitors did not appear to exert a significant cardiotoxic effect in a recent meta-analysis,[14] although long term data on cardiac safety are still missing. On the contrary, both non-steroidal and steroidal anti-aromatase agents may reduce bone mineral density and increase the risk of osteoporotic fractures.[15] Periodical bone densitometry and early administration of calcium, vitamin D with or without alendronate or other bisphosphonates may probably reduce this effect. While waiting for the results of prospective trials, the balance of benefits and risks of aromatase inhibitors should be carefully weighted in vulnerable or frail women with symptomatic osteoporosis and/or fractures.

With the exception of node positive and receptor negative disease,[16] the role of adjuvant chemotherapy in elderly women remains uncertain. Since risk of relapse and life expectancy are the two key elements that may or may not justify the use of adjuvant chemotherapy,[17] only selected vulnerable women with very high risk disease should be proposed adjuvant chemotherapy, while those at intermediate risk and all frail patients would not obtain any benefit from chemotherapy due to the higher risk of toxicity and multiple competing causes of death. For women with receptor-negative disease that may be considered vulnerable and 'unfit for conventional chemotherapy', the International Breast Cancer Study Group recently proposed the CASA trial in which women were randomised between bi-weekly liposomal doxorubicin and a control arm which could be observation or metronomic cyclophosphamide/methotrexate according to the preference of each Investigator. Unfortunately, the trial was prematurely stopped due to poor accrual.

Systemic relapse of BC in elderly women is usually managed with different lines of endocrine agents such as aromatase inhibitors and tamoxifen. Fulvestrant, an antagonist of oestrogen-receptor, has recently been added to the available drugs.

Chemotherapy is usually considered only after progression under endocrine agents, or in case of visceral involvement or in women with oestrogen receptor-negative disease. Several trials have assessed efficacy and toxicity of vinorelbine alone[18] or with gemcitabine[19] or liposomal pegylated doxorubicin,[20] monochemotherapy with taxanes [21] or capecitabine[22] in elderly women. In the Italian trial with weekly paclitaxel,[23] all patients underwent a full MGA before treatment and 26.3% were dependent in ADL and therefore should be considered frail. An unplanned subgroup analysis found that Charlson's score, ADL and IADL dependence were not correlated with toxicity, while only ADL dependence was associated with reduced probability of response. Yet, other factors such as pharmacokinetic heterogeneity and poly-pharmacy[24] as well as the presence of a reliable caregiver might strongly influence the tolerability of chemotherapy. Considering that the response rate of BC to chemotherapy is usually over 30%, most vulnerable and some frail women might be treated with at least one line of chemotherapy following some practical recommendations

1. Monochemotherapy preferred
2. Choose cytotoxic drug according to its adverse events and possible interference with concomitant medications (e.g. paclitaxel and vinorelbine are not first choice in the presence of peripheral neuropathy, capecitabine may interfere with warfarin, etc)
3. First cycle at 75% of standard dose, then increase only if well tolerated
4. Early use of haemopoietic growth factors in case of myelosuppression
5. Verify ability of the patient and her caregiver to recognise and treat the adverse events
6. Predispose phone contacts with the patient to ensure physical conditions and compliance to prescriptions.

A future trial should stratify patients according to results of MGA and report different toxicity rates according to pre-treatment levels of functional autonomy and comorbidity.

3. Non-small-cell lung cancer (NSCLC)

Single-agent chemotherapy with vinorelbine was one of the first approaches in elderly patients with advanced Non Small Cell Lung Cancer (NSCLC) since the toxicity profile of this drug was considered to be mild.[25]

The randomised phase III Elderly Lung Cancer Vinorelbine Italian Study demonstrated the first evidence of the advantage of single agent chemotherapy compared to best supportive care.[26] Also, the role of gemcitabine in this setting was

confirmed by several phase II trials specifically designed for elderly patients. Weekly regimens of taxanes (paclitaxel and docetaxel) administered as single agents have also demonstrated both activity and tolerability in the treatment of advanced NSCLC.

The first largest phase III combination chemotherapy trial compared the combination of vinorelbine and gemcitabine with single-agent chemotherapy with gemcitabine or vinorelbine.[27] Combination chemotherapy did not improve any outcome with increased toxicity. In the absence of specific studies on frail patients with NSCLC, if an active approach in some cases is believed to be useful, single agents should be the preferred option.

The benefit of platinum-based combination chemotherapy has still to be proven by prospective clinical trials specifically designed for elderly patients. The evidence to support the use of platinum agents only comes from several retrospective analyses of the elderly subgroup and are affected by a high risk of selection bias.[28] Since cisplatin administration can be associated with significant nephrotoxicity, ototoxicity and neurotoxicity, its administration should be avoided in frail patients.

Carboplatin, compared with cisplatin, causes lower rates of emesis, nephrotoxicity, and neurotoxicity, therefore representing an appealing alternative for platinum-based chemotherapy. In fact, phase II studies of combination chemotherapy based on modified schedules of carboplatin (low-dose or weekly administration) in older patients have shown a reasonable level of activity and tolerability.

Among targeted therapies, the EGFR inhibitors erlotinib and gefitinib showed to be active and well tolerated as first-line treatment in elderly advanced NSCLC patients. Therefore, these drugs are a potentially ideal treatment for vulnerable and even frail elderly patients due to less toxicity to normal tissues and the available oral formulation.[29,30] Other promising biologic drugs such as the multitargeted agents ZD6474 and sorafenib and the m-TOR inhibitors RAD001 are under investigation.

4. Prostate cancer (PC)

More than 70% of cases of prostate cancer are men $\geqslant$70 years but only 39% of these patients are expected to die directly from this disease.[31]

Distribution of vulnerability and frailty in these patients is largely unknown and strongly biased by the type of cohort in which some form of MGA is carried out. A mini-MGA revealed ADL dependence in 66% of 60 elderly PC patients followed within a Geriatric Oncology Programme in Lyon, at least one serious comorbidity in 75%, cognitive disorders in 45% and malnutrition in 65%.[32] The abbreviated Vulnerability Elders Survey (VES-13) was recently administered to 50 men undergoing Androgen Deprivation Treatment (ADT) at the University of Chicago. Fifty percent of patients had a score of 3 or more, which was demonstrated to correlate with impairment in two or more of the standard tests of MGA. The VES-13 survey (8) may be a valid tool to identify vulnerable patients who are at higher risk of developing functional decline and/or death due to comorbidity, cancer itself or oncological treatments.[33]

The use of ADT increases with advanced age, either in substitution of curative treatment or for a relapse of a tumour resected (or treated with radiotherapy) at younger age. Elderly patients are believed to be at higher risk of developing the well-known adverse events such as sarcopenia, fatigue, reduced physical activity[34] which may strongly compromise the quality of life and accelerate the development of frailty, as recently reviewed by Bylow et al.[35] Since the time of starting ADT (early versus delayed) does not appear to have a strong impact on ultimate survival,[36] delay of treatment is a reasonable option in functionally impaired patients with indolent disease (low tumour burden, low Prostate Specific Antigen (PSA)-doubling time, asymptomatic). Then, when ADT has to be started, promotion of physical exercise and prevention of osteoporosis may probably reduce the severity of ADT adverse events in vulnerable patients with preserved functional autonomy.

In case of bone or visceral progression of disease, there are reports that elderly patients may benefit from weekly docetaxel chemotherapy as well as younger adults, with comparable rates of haematological and extra-haematological toxicity,[37] although fatigue may often impose premature interruption of treatment. Unfortunately, current clinical trials in elderly patients do not encompass geriatric assessment before chemotherapy administration. However, treatment of vulnerable patients requires careful initial health status evaluation, unremitting monitoring of adverse events with appropriate dose reductions, while frail patients should probably never receive cytotoxics.[38]

SIOG guidelines for administering bisphosphonates in the elderly, focusing mainly on renal safety, have recently been made available.[39] With the exception of bedridden frail patients or those with a very short life expectancy, zoledronic acid or ibandronate may be safely administered to vulnerable and also frail patients, and performing the infusion at patient's home would eliminate the discomfort of monthly access to hospital.

5. Colorectal cancer (CRC)

An effective reduction in the occurrence of either a local or distant relapse of colorectal cancer (CRC) may be of major importance for patients over the age of 70 or 80, as their life expectancy largely exceeds the time in which appearance of metastatic disease would compromise their survival.

Adjuvant chemotherapy significantly improves survival in the elderly (hazard ratio of 0.66). The observed benefit is similar to that reported in randomised trials among younger patients[40] even if the principal limitation of randomised trials (differently by observational data) concerns their potential applicability to the general population of elderly patients. As a result of exclusion criteria and screening, elderly patients who entered clinical trials are in fact a selected group, with good performance status and cognition and limited numbers of coexisting conditions. In the subgroup of octogenarians (only 0.7% of patients analysed) who are robust enough to meet typical protocol-eligibility requirements, the data offer no clear contraindications to therapy. In the light of these results it is reasonable to consider chemotherapy with 5-Fluorouracil (5FU) by bolus and continuous infusion (c.i.) and Leu-

covorin (LV) ± oxaliplatin in nearly all vulnerable patients with resected node positive colon cancer, without a significant increase in toxic effects. Vulnerable cardiopathic patients or patients with hypertension might benefit with either 5FU and LV by bolus alone or capecitabine. Adjuvant chemotherapy may be reasonably withheld in frail individuals with multiple comorbidities, malnutrition and poor social support.

Systemic chemotherapy in metastatic disease may prolong survival, decrease tumour-related symptoms, improve general well-being or maintain it at a higher level for a long period of time, but quality-of-life improvements and subjective responses may be the most important objectives for elderly patients.[41,42] 5-FU by c.i. may turn out to be superior to bolus regimen (except for cardiopathic patients who may profit by bolus 5FU/LV); the addition of irinotecan or oxaliplatin improves more and more patients' outcomes. Oral fluoropyrimidine may be useful for those patients refusing central venous catheter. Vulnerable elderly patients may receive these drugs as fit patients but they need more attention regarding their physiological, psychological and physical profiles according to MGA.[3] Age in itself should not be a limit for the introduction of bevacizumab (anti VEGF) or cetuximab (anti-EGFR): limitations for the use of these antibodies should be the same which doctors usually apply to the adults.

In the complex balance of costs/advantages for frail patients, palliative chemotherapy could be avoided.

6. Aggressive Non-Hodgkin's Lymphoma

Patients with aggressive Non-Hodgkin's Lymphoma (NHL) are most commonly found in the older age category. The adverse prognostic value of age cannot be explained solely by biology and most probably reflects the role of comorbidity and other age- related conditions through reduction in chemotherapy dose intensity. To reduce the risk of toxicity without decreasing treatment activity, several regimens have been tested in patients older than 70 years.[43] Although most of them were inferior to standard Cycophosphamide-Doxorubicin-Vincristine and Prednisone (CHOP), these trials deserve merit for having shown that such a disease, even in vulnerable patients, can be treated in the framework of a controlled study. Only the addition of Rituximab to CHOP (R-CHOP) has been shown to improve outcome in elderly patients.[44]

At present then, rather than trying to develop new regimens for older persons, MGA tailored treatment plans should be developed and applied. MGA also helps to show how patients can be supported to overcome their deficits. In several studies on elderly patients with NHL, the entire items of MGA or some of its components (comorbidity, IADL, ADL) have been used in order to determine their correlation with increased toxicity and poorer outcome.[45] Attempts have also been made in another study to tailor treatment taking into account MGA[46] or to devise a specific treatment for frail patient identified with this tool .[47] Also, the EORTC Lymphoma Study Group has adopted a functional definition of frailty through evaluation of performance status, renal and cardiac functions, haematological status and comorbidities.

In conclusion, the majority of medical oncologists and haematologists in Europe involved in cooperative research in this field are aware of the need of sensitive tools to subdivide older patient in the aforementioned 'geriatric' categories. Although at present solid information concerning treatment of vulnerable and frail patients with aggressive NHL is lacking, whenever possible, these cases should be treated with R-CHOP at initially reduced doses.

7. Conclusion

There is at present a general agreement that tumours in the elderly need a peculiar approach involving some form of MGA before therapy.

To spare time some simplified tools are now under investigation in order to screen (in an equivalent way to the MGA) and to identify those older cancer patients needing a modified approach to the antineoplastic therapy. These tests are essentially the abbreviated VES-13,[8] the shortened version of the MGA adopted by Overcash[9] and the eight items tool based on the mini-nutritional assessment and age.[10]

In this article an effort has been made to show how, in presence of vulnerability or frailty, the therapeutic approach should be modified and adapted in the main tumour types.

Unfortunately, most of our considerations do not derive from clinical trials, since these are conducted in a selected group of older patients with minimal comorbidity and without disability, but rather from the clinical experience. We know that in dealing with the treatment of frail and vulnerable older patients we are in the realm of an enlightened empiricism, but with this article, showing how little we know, we would like to stimulate specific trials in vulnerable and frail patients. Enrolling older patients in clinical trials is believed to be more difficult and in fact it has been shown that the percentage of older patients entering into clinical trials is consistently inferior to that of younger adults. More resources and a better organisation in the field of Geriatric Oncology are needed. In some countries, such as in the United States and in France, these needs have been well understood and a robust funding policy in this field has been generated to support the clinical investigators, while in other European countries the problem of clinical trials in the older population is still lagging behind.

Conflict of interest statement

None declared.

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