

Review

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Quality of Life in elderly patients with cancer

Massimo Di Maio and Francesco Perrone*

Address: Clinical Trials Unit, National Cancer Institute, 80131 Naples, Italy

Email: Massimo Di Maio - dimaiomax@libero.it; Francesco Perrone* - fr.perrone@agora.it

* Corresponding author

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Abstract

The incidence of most types of cancers is age-dependent and the progressive ageing is rapidly increasing the number of elderly people who need treatment for cancer. Elderly patients present peculiar characteristics that make the choice of the correct treatment more difficult and these patients are often undertreated. Moreover, elderly patients are largely underrepresented in cancer treatment trials, and this makes the experimental evidence on this topic even weaker. Health-related Quality of Life (QOL) has been considered as one of the hard end-points for clinical cancer research, and treatment of elderly cancer patients represents a typical situation where its assessment can be particularly useful, because the expected toxicity of treatment could be relevant in the discussion of the treatment choice. However, QOL assessment in the elderly is complicated by several unresolved methodological problems (higher frequency of illiteracy, worse compliance with the questionnaires, concomitant diseases, use of instruments not validated in the aged population). Conduct of clinical trials dedicated to elderly patients is now encouraged but there are few published studies. Advanced non-small-cell lung cancer is one of the fields with the largest amount of research on QOL in elderly patients. The ELVIS study demonstrated the efficacy of single-agent chemotherapy, both in terms of QOL and of survival. The MILES study, in which combination chemotherapy was not superior than single agents, showed that baseline QOL is a strong prognostic indicator in these patients. QOL of patients with breast cancer has been another important field in clinical research over the last decades, and interest on this topic in elderly patients is growing, from loco-regional to palliative treatment.

In conclusion, some steps have been done in clinical cancer research dedicated to elderly patients, and the role of QOL assessment in this setting is important. However, many methodological problems must be resolved, in order to obtain reliable and useful results. A QOL assessment could also be useful for elderly patients in clinical practice, where it could improve patient-clinician communication: a wider application of properly selected instruments should be recommended.

Review

Elderly patients and cancer between clinical practice and research

If current incidence rates will not decrease, in the next fifty years the number of people diagnosed with cancer is

expected to double, solely due to the progressive ageing of the population [1]. Ageing is rapidly affecting the median age of all Western populations, mostly due to the reduction in birthrate, coupled with the increased life expectancy (figure 1). This demographic phenomenon is rapidly increasing the number of people who are diagnosed and

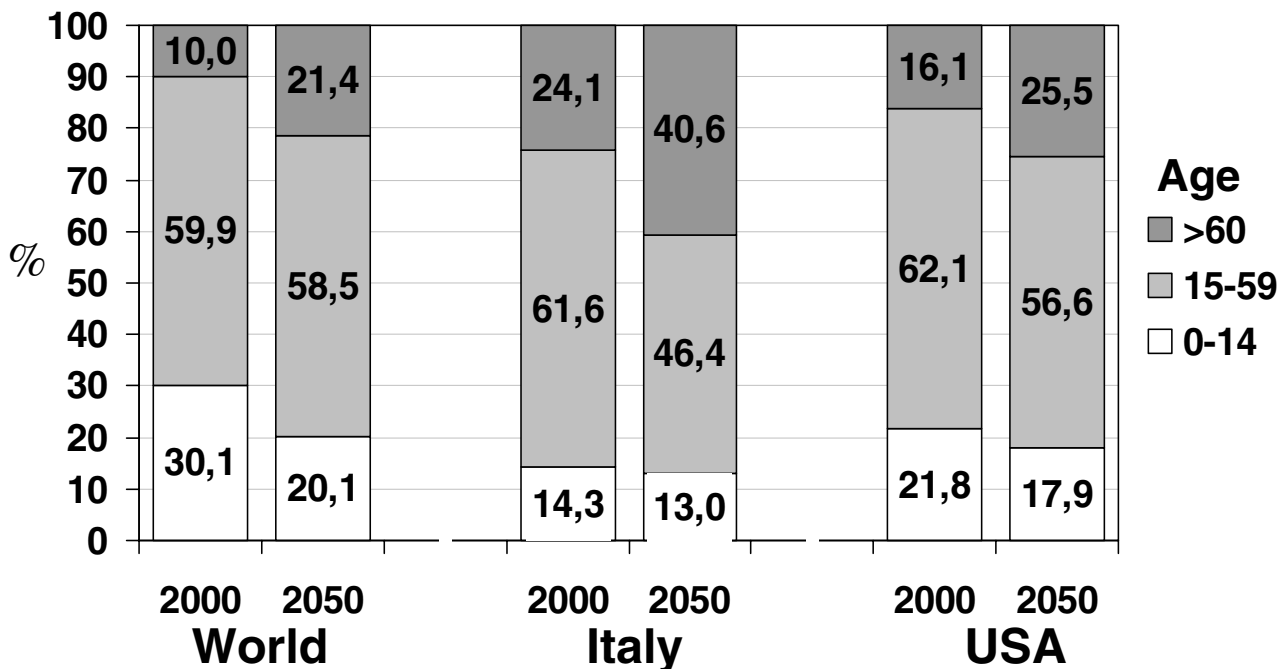


Figure 1
 Percentage distribution of the population in selected age groups, in 2000 and 2050. *Data from: Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat (2003). World Population Prospects: The 2002 Revision. Highlights.* New York: United Nations.

treated for cancer, because the incidence of most types of cancers is age-dependent and the risk of developing a tumor is progressively higher with increasing age [2].

Elderly patients present peculiar characteristics [3,4] that make the choice of the correct treatment more difficult, often exposing these patients to the risk of being under-treated [5]. Although chronological age is not necessarily equivalent to biological age, ageing determines physiological changes in organ functions and pharmacokinetics. Furthermore, concomitant diseases are very frequent, significantly affecting the functional status and the general health condition, in addition to tumor symptoms. Therefore, a correct approach to elderly people with cancer should not leave out a comprehensive geriatric assessment, in the attempt to better predict the prognosis of the

patient and the risks associated with specific treatments [6].

Despite the universal recognition of the importance of clinical trials to inform clinical practice and to guide therapeutic decisions, it has been repeatedly reported that elderly patients are largely underrepresented in cancer treatment trials [7-9]. The first major survey was published in 1999 by Hutchins *et al* [7]. They analyzed 164 clinical trials conducted by the South West Oncology Group, for a total of 16.396 patients, comparing the proportion of elderly patients enrolled in clinical trials with the proportion of elderly people diagnosed with cancer in the general population. They reported that 25% of the trial population was over 65, compared with 63% of the overall cancer patient population. Another similar survey

has been recently presented at the 39th Annual Meeting of the American Society of Clinical Oncology in Chicago [9]. Authors analyzed data from 29,350 patients enrolled in trials conducted over seven years (from 1995 to 2002) dealing with treatments for six different types of cancer. Similarly to the other surveys, the percentage of cancers of each type that were diagnosed in older patients in the general population was compared with the percentage of elderly patients enrolled in clinical trials for each cancer. A great disparity between percentages of elderly patients in the general population and in clinical trials was found for pancreatic cancer (71% vs 33%), leukemia (54% vs 24%), colorectal cancer (70% vs 41%), lung cancer (67% vs 35%), with smaller but yet statistically significant disparities for ovarian (44% vs 31%) and breast cancers (49% vs 45%). It is worth to be noted, although predictable, that underrepresentation was particularly notable for patients older than 75 years.

This phenomenon can significantly affect the generalizability of trials' results, that largely depend upon whether subjects enrolled in clinical trials are fully representative of the entire spectrum of patients suffering from that disease.

The role of Quality of Life assessment in cancer

Health-related Quality of Life (QOL) has been recommended as one of the hard end-points for clinical cancer research [10]. Use of QOL instruments may be particularly appropriate when treatments are not expected to achieve significant advantages in terms of overall survival (e.g. advanced non-small-cell lung cancer): in the case of metastatic cancer, guidelines from the American Society of Clinical Oncology state that a treatment can be recommended even without an improvement in survival, if it demonstrates an improvement in terms of quality of life [10]. QOL assessment can also be useful when the expected toxicity of treatment (either due to treatment itself or to characteristics of patients) could be so relevant to put into discussion the treatment choice. Treatment of elderly cancer patients represents a typical such case.

In addition, it should not be forgotten that patients might have a preference for a treatment potentially able to

improve their quality of life rather than their survival [11]: when asked to choose between supportive care and chemotherapy, only 22% of the patients chose chemotherapy for a hypothesized survival benefit of 3 months. Conversely, 68% patients chose chemotherapy if it substantially reduced symptoms, even if no significant effect on survival was expected.

Methodological issues of Quality of Life assessment in the elderly

A good quality of life should be a primary goal in the treatment of elderly patients with cancer, but to date very few studies have specifically focused on this topic [12,13]. Thus, assessment of health-related QOL in elderly patients with cancer remains a controversial area of research, with specific implications, both in measuring and in evaluating the results (table 1). This may have discouraged the planning of clinical trials in this setting [13]. All the methodological problems related to QOL evaluation are somewhat magnified in the elderly. Aged patients may suffer from a higher proportion of illiteracy, and this may translate into increased difficulty to correctly understand the questionnaires administered [14]. Furthermore, the real impact of cancer symptoms and the harms and benefits of specific treatments in terms of quality of life may be confounded by the comorbidities, that are typically frequent and clinically significant in this category of patients [4]. Elderly patients have shown lower compliance to QOL questionnaires when compared to younger counterparts [15], and this creates the problem of a correct interpretation of data, given that the pattern of missing data is most likely non-random. This problem can be particularly evident for tumors characterized by a poor short-term prognosis and a rapid deterioration of patients' conditions. It has been shown, in elderly patients affected by advanced non-small-cell lung cancer, that the baseline scores are worse for the patients who are going to fill in fewer questionnaires, as compared to the patients who fill in all the planned QOL assessments [16]. These data clearly suggest that the missing data would probably be the worst ones. Of course, this can lead to biased estimation of QOL in clinical trials, if missing data are not equally distributed among study arms.

Table 1: Methodological problems of Quality of Life (QOL) evaluation in the elderly

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- Higher proportion of **illiteracy** as compared to younger patients
 - Presence of **cognitive disorders** with difficulty to understand QOL questionnaires
 - Presence of **comorbidities** potentially confusing the real impact of cancer and treatment on QOL
 - Use of QOL instruments needs **validation** in elderly patients
 - Analysis of QOL data from subgroups of elderly patients enrolled in clinical trials without upper age limit suffer from **selection bias**.
-

As for clinical practice, a QOL instrument can be a useful clinical tool in conducting a thorough medical assessment [17]. This can be particularly true in the care of the older patient with cancer.

When using QOL instruments in an aged cancer population, validity and reliability in this category of patients of instruments not specifically designed for elderly should be demonstrated [18]. It cannot be assumed that a QOL instrument validated in younger individuals is equally appropriate for use in elderly patients, who are likely to have different values and perceptions when compared with younger patients. Some attempts have been made to develop and validate QOL instruments specifically developed for the geriatric population [19], or to validate widely used instruments in elderly patients. For example, one of the most widely used QOL instruments, the Functional Assessment of Cancer Therapy General Scale (FACT-G), has been recently validated in elderly cancer patients [20]. FACT-G total score and subscores were compared with the mixed aged cancer patient normative group of Cella et al. [21]. Authors' conclusions were that FACT-G proved a valid and reliable instrument, not biased by patients' age. Higher scores on the FACT-G questionnaire were reported by subjects with higher Eastern Cooperative Oncology Group Performance Status (PS), that is expression of the physician's assessment of the patient's conditions. For example, subjects with PS0 had a mean total FACT-G score of 87.9, compared to a mean score of 59.0 for patients with PS3. Other QOL instruments, the SF-20 and the Rotterdam symptom checklist, have been validated in older patients affected by aggressive non-Hodgkin's lymphoma [22].

In the next section, evidence regarding QOL in elderly patients affected by two of the most frequent types of tumors, non-small-cell lung cancer and breast cancer, are reviewed.

Quality of life in elderly patients with non-small-cell lung cancer

The majority of patients affected by lung cancer are unfortunately diagnosed at advanced stage, when palliative treatment is the only therapeutic option. Standard treatments available to date, consisting of chemotherapy with cytotoxic drugs, are far from being satisfactory, achieving very small survival benefits encumbered by a not negligible toxicity. Therefore, non-small-cell lung cancer (NSCLC) can be considered paradigmatic of a large field of oncologic research in which particular attention should be paid to QOL assessment, especially in elderly patients [23].

The ELVIS study (Elderly Lung cancer Vinorelbine Italian Study), a randomized phase III trial conducted by our

cooperative group, was published in 1999 [16]. This trial represented a very important step in this field, because it was specifically designed for elderly patients. Patients older than 70 years affected by advanced NSCLC were randomized to receive best supportive care alone or best supportive care plus chemotherapy (single-agent vinorelbine at the dose of 30 mg/m², days 1 and 8 every three weeks for a maximum of six cycles). The main end-point of the study was QOL and for its assessment the European Organization for Research and Treatment of Cancer (EORTC) core questionnaire (QLQ-C30) and lung-cancer-specific module (QLQ-LC13) were used. The trial began in April 1996. During the conduct of the study, however, investigators, although blinded to the results, were increasingly reluctant to randomize patients, because they could have been assigned to a control arm without chemotherapy. Furthermore, an increasing number of patients refused to participate in the study, explicitly asking for chemotherapy. Accrual rate had consequently dwindled from eleven to five patients per month, and the enrollment of the study was interrupted in November 1997, before reaching the planned sample-size.

The effect of vinorelbine on QOL was evaluated by fitting a linear mixed model for each EORTC scale, taking into account all the QOL assessments (baseline; before each course of chemotherapy in the vinorelbine arm and before each follow-up visit in the control arm). QOL results showed several significant differences between the two arms, related to the side effects of chemotherapy and to its benefits in terms of tumor symptoms and functioning scales. Consistent with the expected toxicity profile of vinorelbine, patients receiving chemotherapy reported worse scores on the scales relating to nausea and vomiting, constipation, peripheral neuropathy and hair loss. However, patients treated in the vinorelbine arm scored clearly better than controls on many subscales: global health status/quality of life, four functioning scales (role, cognitive, social and physical functioning), fatigue, pain, dyspnea, cough, hemoptysis, pain in the chest and shoulder, pain in other sites and need for analgesia (figure 2). With 161 patients analyzed, those assigned to vinorelbine plus best supportive care had a significantly longer survival (28 weeks vs 21 weeks, log-rank test $p = 0.03$) and had greater chance to be alive at six months (55% vs 41%) and at one year (32% vs 14%) than those who did not receive chemotherapy. When adjusted by tumor stage and patient's performance status, the relative risk of death in the group treated with chemotherapy was 0.65 (95% CI: 0.45–0.93; $p = 0.02$).

The results of the ELVIS trial have demonstrated the benefit of single agent chemotherapy with vinorelbine in elderly patients affected by NSCLC. In order to test if the

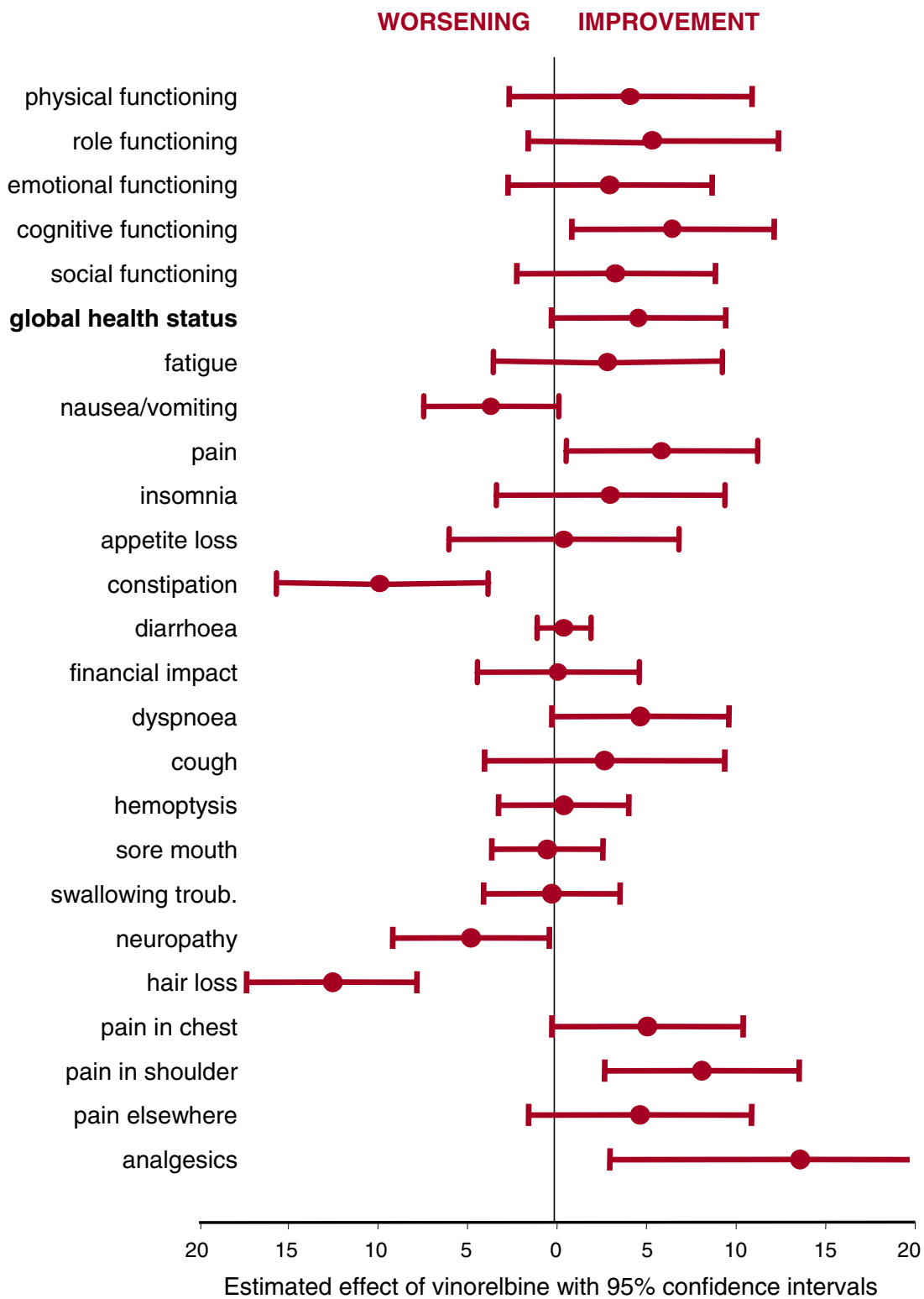


Figure 2
 Estimated effect of vinorelbine on Quality of Life of elderly patients with advanced non-small-cell lung cancer.

polichemotherapy could have been more effective than single agents in the treatment of these patients, we designed and conducted, within the same cooperative group, another phase III trial, the MILES trial [24], dedicated to the same patients' population of the ELVIS study. The combination of vinorelbine (25 mg/m²) plus gemcitabine (1000 mg/m²) was compared to single-agent vinorelbine (30 mg/m²) or gemcitabine (1200 mg/m²). All drugs were given on day 1 and 8 every three weeks, for a maximum of six cycles. Although overall survival was the primary end-point of the study, a QOL assessment was planned, using the same instruments of the ELVIS trial (EORTC QLQ-C30 and LC13). At the end of the enrolment, 698 patients were analyzed: median age was 74 years, and 275 patients (39%) were 75 years or older. Combination chemotherapy proved slightly more toxic than monochemotherapy, but unfortunately did not show any advantage as compared with each single drug. EORTC questionnaires at the end of the third cycle of chemotherapy were completed by 346 of the 585 patients (59%) who had completed the questionnaires at baseline. There were no significant differences in functional and symptoms scales between patients assigned to the combination and those assigned to single-drug treatments. Only hair loss, as estimated by the patients, was significantly worse with vinorelbine plus gemcitabine than with gemcitabine ($P = 0.03$).

Interestingly, a secondary analysis of the MILES study [25] has evaluated the prognostic role of baseline QOL (EORTC C30 global QOL score – items 29 and 30) in the elderly patients, together with the prognostic role of geriatric functional status (ADL – activities of daily living – and IADL – instrumental activities of daily living). ADL status, IADL status and baseline QOL score were added to a predefined multivariable model: ADL status was not an independent prognostic factor for survival, IADL status showed independent prognostic role only for worst scores, while baseline QOL score was a strong and independent prognostic factor for survival, even when controlling for performance status, histotype, number of sites of disease, size of the Institution, age, gender, stage and treatment. These results confirm also in elderly patients the strong prognostic role of self-assessed quality of life in patients with advanced lung cancer [26].

In the last years, several authors have retrospectively analyzed the outcomes of elderly patients, compared with those in younger patients, in clinical trials for NSCLC patients whose eligibility criteria did not have an upper limit for age. The ECOG 5592 randomised trial compared three platinum-based chemotherapy regimens for NSCLC [15]. QOL was assessed by FACT-Lung questionnaire. Younger and older patients showed similar baseline QOL scores, with equivalent decline over time in functional

well-being, and showed comparable outcomes in terms of response rates, toxicity and survival. The authors conclude that advanced age itself should not preclude standard NSCLC treatment. However, the concern about worse compliance to QOL questionnaires by elderly patients seems to be confirmed in this trial, because only 21.5% of elderly patients completed the QOL questionnaire administered after 6 months, compared with 37.2% of younger patients: the authors themselves recognize that this significant difference most likely means that the entire population of elderly patients was actually worse than suggested by the data.

Quality of life in elderly patients with breast cancer

Health-related QOL of patients with breast cancer has been an important topic in clinical research over the last decades [27]. However, also for this tumor, there are very few data derived from prospective clinical trials specifically dedicated to elderly patients, and most of the knowledge on this topic is derived from subgroup analysis of studies conducted in postmenopausal women. This is disappointing, because a high proportion of newly diagnosed breast cancers affect elderly people, and better scientific evidence on the correct management of these patients would greatly help the daily clinical practice.

In the survey by Talarico *et al* [9], addressing the underrepresentation of elderly patients in clinical trials, attention has been dedicated to study the impact on this phenomenon of the different types of treatments. The authors found that older women with breast cancer are just as likely as younger patients to enter studies of hormonal treatments, which typically have mild side effects, but they are much less likely to get into studies of chemotherapy, that is expected to more negatively affect QOL. The considerations that make elderly patients at higher risk of undertreatment, are no different in the clinical practice either. An Italian survey [28] on the treatment modalities of nearly three thousand women affected by breast cancer with metastatic lymph-nodes, showed that fewer elderly patients had received standard radiation treatment after breast conservation, and that adjuvant chemotherapy was proposed to only 6% of the patients, compared to 35% of the younger counterpart.

Here again, studies specifically evaluating the safety and efficacy of different therapies in elderly patients would give clear answers on what is worth and what is not, and what is safe and what is not, without leaving the choice to personal, subjective decisions that may be reasonable but remain non evidence-based. QOL would probably have an important role in trials dedicated to each of the steps in the treatment of elderly patients with breast cancer, from the choice of the best modality of loco-regional treatment

for early disease to the choice of the best palliative treatment for metastatic patients.

An example of the role of QOL assessment in elderly patients with early breast cancer comes from a study dedicated to breast-conserving treatment [29]. Age itself should not be a contra-indication for conservative surgery, but retrospective studies have indicated that elderly patients are less likely to be treated conservatively. The EORTC 10850 randomised trial analyzed survival and QOL in elderly patients (>70 years) with early breast cancer, undergoing mastectomy or tumour excision plus tamoxifen. A QOL questionnaire consisting of 36 items, covering nine different domains, was filled out by 136 patients (65 in the mastectomy arm and 71 in the local excision arm) during the first year of follow-up. No significant difference in the duration of survival between the two treatment arms was observed in the subgroup of patients included in the QOL sub-study. Patients assigned to tumour excision and tamoxifen did not differ from those undergoing mastectomy in terms of fatigue, emotional functioning, fear of recurrence, social support, physical functioning and leisure time activities. However, conservatively treated patients reported fewer arm problems and a borderline significant benefit in body image. In conclusion, QOL appears somewhat better after conservative treatment, and the authors encourage the use of this approach also in older patients.

The study by Crivellari et al. [30] is an example of the role of QOL assessment in the evaluation of adjuvant chemotherapy. They analyzed the data collected as part of the International Breast Cancer Study Group Trial VII, in order to evaluate the risk/benefit ratio of adjuvant chemotherapy for postmenopausal women with operable breast cancer with metastatic axillary lymph-nodes. The study compared tamoxifen alone for 5 years versus tamoxifen plus three cycles of classical CMF (cyclophosphamide, methotrexate, fluorouracil). QOL was measured using linear analog self-assessment scales for coping, physical well-being, mood, and appetite. A higher number of older women experienced severe toxicity compared with younger patients, but the subjective burdens of treatment measured by QOL were similar for the two age groups. This finding was explained by the authors with the tendency of elderly patients to complain less and endure symptoms better.

As for advanced disease, there are several reasons to consider QOL assessment of potentially great importance in elderly patients. Unfortunately, when reviewing literature on clinical research about this setting of disease to date, it has been noted that QOL analysis rarely provided information beyond that obtained from more traditional medical outcomes, like toxicity [27]. Its use could proba-

bly be recommended in the case that one of the treatments is expected to produce a very mild toxicity, or to have significantly different side-effects, that could determine a sensible difference between treatments in terms of QOL.

Conclusions

There is a need for clinical trials specifically dedicated to elderly patients, because results are probably more generalizable to clinical practice than subgroup analysis of studies without upper age limit. Studies like ECOG 5592 [15], or the CALGB 9730 [31] have eligibility criteria designed for adult patients and the enrolled elderly patients just represent a selected subgroup. These patients probably carry a better prognosis and higher treatment compliance than the whole elderly population. Information derived from this kind of selected patients, particularly in the case of trials with aggressive and toxic treatment approaches, can be misleading and dangerous if generalised to clinical practice [32]. Investigators from the Food and Drug Administration are encouraging the development of strategies to increase the number of older patients enrolled in cancer clinical trials [9] and are promoting prospective trials designed specifically for those aged 65 and older.

Quality of Life has become a common endpoint in clinical research on cancer treatment. Scientific community is often facing the problem of underrepresentation of elderly patients in clinical trials, and it seems easy to predict for the near future a growing number of studies dedicated to elderly patients, probably with a majority of these studies providing a Quality of Life assessment. As described, this assessment in the elderly is still complicated by several unresolved methodological problems (frequency of illiteracy, worse compliance with the questionnaires, influence of concomitant diseases, use of instruments not specifically validated in the aged population). Therefore, planning of these trials should be made with caution.

The role of a systematic Quality of Life assessment in clinical practice is very important. Comprehensive assessment of the elderly cancer patients, also based on self-report methodology like Quality of Life questionnaires, has been proven feasible and useful in some settings [33]. Quality of Life assessment could be useful not only because it has a strong prognostic power for survival of patients, but also to allow for the discussion with the patient of the answers given to specific items of the questionnaire. This discussion may help the clinician to better assess the overall burden of symptoms suffered by the patient and the relative importance given to each of them, in order to better plan and modify the best treatment strategy.

In conclusion, some steps have been done in the field of clinical cancer research dedicated to elderly patients, and

the role of Quality of Life assessment in this setting is promising. However, many methodological problems are still to be resolved, to allow the best use of these potentially useful instruments. A Quality of Life assessment in clinical practice seems particularly useful for elderly patients, allowing better communication between patient and clinician, and a wider application of properly selected instruments should be recommended.

Authors' Contributions

Both authors planned the manuscript. Massimo Di Maio conducted the literature review and drafted the manuscript. Francesco Perrone revised the manuscript. Both authors approved the final version.

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