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## Original research article

# Do we protect or discriminate? Representation of senior adults in clinical trials

Joanna Kaźmierska <sup>a,b,\*</sup><sup>a</sup> Radiotherapy Department II, Greater Poland Cancer Center, Poznan, Poland<sup>b</sup> Electroradiology Department, University of Medical Sciences, Poznan, Poland

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## ABSTRACT

**Aim:** The analysis of barriers responsible for low recruitment of older patients in clinical trials and presentation of possible solutions are the subject of this review.

**Background:** Europe's population is ageing, and the group of people who more frequently develop neoplasms increases. Oncologists are confronted with a new challenge – how to treat cancer in this group of patients, especially considering the lack of Evidence Based Medicine (EBM) guidelines for treatment of cancer in the elderly population.

**Materials and methods:** Medline search and analysis of studies published between 1999 and 2012, containing key words: senior adults, cancer, elderly in clinical trials.

**Results:** Detailed analysis of relevant studies demonstrated that senior adults are under-represented in clinical trials. Moreover, there is a lack of trials exclusively designed for this heterogeneous group of patients. The analysis of reasons for low recruitment of older patients in clinical trials revealed barriers dependent on patient's and physician's attitudes as well as institutional and logistic problems.

**Conclusions:** It is necessary to widen the scale of trials of all phases in the group of seniors with appropriate assessment of toxicity. This will allow a proper stratification and obtaining representative groups for statistical analysis and credible trial results. Another priority is the design of trials dedicated exclusively to the elderly.

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## 1. Background

A well-designed randomised clinical trial (RTC) constitutes one of the most important methods of testing therapeutic hypotheses and provides level I evidence for the justification of a therapeutic process.<sup>1</sup> Such trials form the basis of meta-analysis which underlies the standards of treatment and

enables patients to be treated following the guidelines of Evidence Based Medicine (EBM). However, if one analysed the groups of patients included in RTC in oncology, it would turn out that the representation of certain groups in the trials is unsatisfactory. A case in point here is the group of elderly patients which, according to an arbitrary definition, encompasses people aged over 65. Prevalence of particular cancers in senior adults is different than in younger population. Most

\* Correspondence address: Radiotherapy Department II, Greater Poland Cancer Center, Garbary St 15, Poznan, Poland. Tel.: +48 61 8850 750; fax: +48 61 8850 751.

E-mail address: [joanna.kazmierska@wco.pl](mailto:joanna.kazmierska@wco.pl)

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frequently diagnosed cancer in people over 65 is prostate cancer followed by colorectal cancer as well as brain and breast cancer.<sup>2</sup> As research demonstrates, only 22% of patients over 65 participate in all cancer clinical trials and among people aged over 70 the percentage falls to a mere 8%.<sup>3–6</sup> Significant differences were demonstrated between participation in cancer site-specific trials. Lewis et al. demonstrated in their meta-analysis that the elderly were significantly underrepresented in phase III melanoma, breast, colorectal, head and neck, lung, central nervous system and uterine cancer trials.<sup>6</sup> Senior population was adequately represented in early and late prostate cancer related trials and especially in breast cancer hormonal treatment trials.<sup>6,7</sup>

This problem is receiving more and more interest as it concerns a growing number of patients – Europe's population is ageing at an ever faster rate.<sup>8</sup> Thus, oncologists are confronted with a new challenge – how to treat cancer in this group of patients. Due to the lack of data concerning the treatment of older cancer patients, this group is often excluded from standard aggressive treatment, especially adjuvant. What is more, senior patients form a considerably heterogeneous group – following solely the criterion of age results in having both fit as well as vulnerable and frail individuals in the same group. Hence, it is not possible to refer to this group the results obtained in the group of younger persons, which is relatively homogeneous in terms of health status.

The multidimensionality of the problem is responsible for the fact that physicians are not only unwilling to include the elderly in ongoing clinical trials but they are also afraid to apply standard treatment, especially adjuvant, considering it to be too aggressive. Aparicio's research in which he proved that 52% of patients with colorectal cancer had sub-standard treatment can serve as an illustrating example.<sup>11</sup>

However, it is the adjuvant therapy that has a positive effect on the survival rate and the time to recurrence in the case of patients with resected colon cancer.<sup>12</sup> Folprecht presented similar results concerning the treatment of metastatic colorectal cancer by means of standard chemotherapy 5FU: the survival rates in the case of older patients were comparable to those of younger ones.<sup>13</sup> Likewise, the application of standard, more aggressive adjuvant treatment in women with breast cancer who were over 65 proved superior to less aggressive treatment in the context of survival.<sup>14</sup> The results of the research indicate that a significant number of senior patients derive significant benefit from more aggressive methods. Thus, seniors should also be included in experimental clinical trials, provided that their health state, physiological reserves, and comorbidities will be correctly assessed.

Recently, the National Comprehensive Cancer Network (NCCN) and the European Organisation for Research and Treatment of Cancer (EORTC) issued first recommendations for treatment of senior adults.<sup>9,10</sup>

## 2. Aim

The analysis of barriers responsible for the underrepresentation of older patients in clinical trials and the design of clinical trials dedicated exclusively to seniors will be the subject of this review.

## 3. Materials and methods

Medline search of peer reviewed studies published between 1999 and 2012 containing keywords: senior adults, cancer, elderly in clinical trials. Reference lists from relevant studies were scanned to identify any additional studies.

Studies included in the review were in English; reports published in the form of abstracts were not included.

Studies reporting reasons or barriers of underrepresentation of seniors in clinical trials of all phases and analysing potential solutions were included into the analysis. Studies without analysis for reasons of recruitment barriers or ones that reported on the absence of all minorities beyond elderly only trials were excluded.

## 4. Results

Medline search identified 13,900 publications evaluating seniors' representation in cancer clinical trials, 106 exploring underrepresentation of elderly in clinical trials. 13 relevant papers analysed and discussed barriers and solutions in recruiting patients over 65 years in research studies.

Reasons for the underrepresentation of elderly in clinical trials could be divided into system-, physician- and patient-dependent<sup>15</sup> and are described below.

### 4.1. Eligibility criteria and trial design.

Until recently, it seemed that one of the basic causes of the underrepresentation of older patients in clinical trials was strict eligibility criteria which specified the maximum age of patients included in the trials. In general, the maximum age for many trials was 65 or 70 years. Nevertheless, the Cancer and Leukaemia Group B (CALBG) trial did not fully confirm this phenomenon – in the trial of adjuvant chemotherapy in breast cancer where there was no age limit, only 8% of female patients included were older than 65 and only 4% were over 70 years of age.<sup>16</sup> In 1989, the FDA recommended not excluding older patients from clinical trials as age in itself cannot be regarded as an eligibility criterion.<sup>17</sup>

Also, seniors are much more often included in cancer trials which look at the late stage of cancer than in early-stage cancer trials.<sup>6</sup> Another alarming observation is that the percentage of elderly patients is small not only in the case of trials concerning basic treatment but also in the trials investigating supportive care – 24% and 21%, respectively.<sup>4</sup> The other factors excluding patients from clinical trials are comorbid illnesses and functional status.

### 4.2. Functional status and comorbidities

The natural processes of ageing influence the functions of many organs and many physiological processes, which in turn can affect negatively the results of trials.

Many trials exclude patients with kidney and liver dysfunctions as well as cardiac failure, which are typical of old age. Such exclusion criteria lower significantly the participation of elderly patients in clinical trials – by about 22%.<sup>18</sup> Moreover,

clinicians themselves are unwilling to propose new experimental treatment which may, because of its toxicity, worsen the state of the already frail patient.<sup>19</sup> Such concerns are often justified, but the assessment of the actual health condition of the senior is a complex matter and cannot be made following only a subjective evaluation of the clinician. Comprehensive Geriatric Assessment (CGA) seems to be the most suitable instrument of thorough evaluation of senior's health.<sup>20</sup>

Comorbid illnesses are an inextricable part of the treatment of older cancer patients.<sup>21</sup> On average, they suffer from 5 co-existing illnesses, including the most frequent cardiovascular and respiratory diseases.<sup>22</sup> Since in many cases we still have too little information about the tolerance of treatment when comorbidities are present, it is necessary to design clinical trials in such a way as to allow for a reliable assessment of the influence these conditions have on the results of treatment and its toxicity and vice versa. Illnesses which impair functioning at old age do not necessarily influence in the same way the results of various oncological treatment methods. Advanced coxarthrosis can serve as an example – it does not affect chemotherapy in a significant way but it may seriously impair the reproducibility of positioning in radiotherapy of the pelvis and increase the risk of serious late effects. In addition, some trials still exclude patients who had cancer in the past, which much more often concerns older patients.

#### 4.3. Polypharmacy and drug interactions

Because of numerous comorbidities, many elderly patients take regularly on average 6 medications a day and the tendency is increasing.<sup>23</sup> The medications taken may interact with oncological drugs, intensify or weaken their effect as well as cause unpredictable severe adverse effects. Therefore, the first step when including a patient in a clinical trial should be a rational reduction of the number of medications by an experienced geriatrician.

#### 4.4. Patients' preferences

Patients' preferences and their possible reluctance to participate in the phase I and II trials were presented by Basche and colleagues on the basis of a survey conducted in the senior groups aged 65–74 and 75 and over. The survey revealed that over 40% of seniors do not perceive any obstacles to their participation in such trials.

The main causes of the reluctance to participate reported by the patients were the logistic issues: the necessary time and assistance required of another person, the necessity to undergo treatment in an academic centre far from their place of residence as well as discontinuation of the treatment by their "own", well known, primary oncologists. Incorporating primary oncologists into the trials was an important condition for 100% of respondents participating in the survey. Seniors, especially older ones, are willing to accept possible side effects of the trial, in particular nausea and vomiting to a lesser extent.<sup>24</sup> It seems, thus, that the obstacles stemming from patients' incertitude are relatively easy to eliminate, e.g. by visiting patients at their homes or organizing transport and care for them, incorporating their primary oncologist and nurse in the trials, providing best supportive care in order to

minimise the negative side effects or the toxicity of experimental treatment. An essential issue for the patients was also appropriate information concerning the proposed trial, adjusted to the patients' perception.

#### 4.5. Physician's factors

It turns out that a number of seniors regardless of their preferences and potential are not offered a chance of participation in clinical trials. A partial explanation of this situation is provided by the survey conducted by Kornblith and colleagues.

There are a number of reasons for physicians' reluctance to include older patients in clinical trials. The major ones include: the concern about excessive toxicity and comorbidities as well as insufficient, in the physician's view, support at patient's home, expected difficulties with understanding the assumptions of clinical trials by patients and greater amount of time necessary to explain the trial to a senior patient. Another significant factor here is logistics: e.g. transportation of a patient to a centre and expected poor compliance. Moreover, a number of health professionals are of the opinion that short survival time should exclude patients from participation in clinical trials.<sup>25</sup>

An additional factor was physicians' lack of knowledge about the availability of a suitable clinical trial for an individual patient. These barriers appear to be relatively easy to overcome by dissemination of information concerning clinical trials among physicians and providing appropriate social and logistic support. On the other hand, the assessment of health status and the reserves of the organism as well as the expected toxicity require collaboration with geriatrician and application of tests and scales dedicated to this assessment.

#### 4.6. Treatment toxicity

The expected excessive toxicity is one of the main reasons why older patients are excluded from clinical trials, in particular the trials where new experimental drugs or radiotherapy treatment are used. Pharmacokinetics of medications taken by older patients varies from the group of younger persons as well as from senior to senior. It is linked to changes in organs and physiological processes which occur in old age. These changes in organs lead to different bioavailability of drugs, especially oral drugs and the decrease in the effectiveness of medications which are activated by liver enzymes. Additionally, kidneys function as well as the rate at which drugs are removed from the organism have a significant influence on the expected toxicity of the therapy.<sup>26</sup> Also the interactions of tested drugs with medications used for comorbid illnesses are important. This results in clinicians' concerns about the unexpected adverse effects of new therapies in older patients, particularly in the case of completely new targeted therapies and their experimental combination with radiotherapy, for example, although evidence exists that senior patients can tolerate molecular targeted therapies as well as younger counterparts.<sup>27</sup>

Adjuvant treatment in seniors constitutes a separate problem as it is frequently considered too toxic for older patients. However, as research demonstrated in the case of solid tumours, such as colorectal or lung cancer,<sup>12,13</sup> older patients did not experience increased toxicity in the trial compared

to the group of younger patients, while beneficial effects on their overall survival were noted. In order to overcome clinicians' views regarding the excessive toxicity of treating older people, it is necessary to carry out a detailed study on dose related toxicity and drug interaction, as well as to conduct a well-designed stratification in trials according to functional status, comorbidities and potential dose modification.

#### 4.7. Supportive care

Supportive care in its wide sense is an indispensable element of modern oncological treatment. Elderly patients, particularly frail, should be provided with thorough care because the success of the trial frequently depends on supportive care. For instance, intense vomiting may cause dehydration and electrolyte disturbance; oral mucositis can lead to food aversion, hypoalbuminemia, malnutrition, etc. Likewise, anaemia and/or leucopenia may result in treatment failures due to hypoxia and infections. Understanding the significance of supportive care during treatment may considerably influence the perception of toxicity by clinicians and, thus, encourage them to include older patients in clinical trials.

## 5. Discussion

In the face of the ageing of societies of Europe and other continents, developing both guidelines and therapeutic recommendations for the growing group of senior patients assumes significance. Are we as oncologists prepared for this? Unfortunately, the lack of knowledge concerning not only detailed physiology of ageing but also cancer itself is the reason why we practically do not have guidelines for such a heterogeneous group of patients as senior adults. Clinical trials constitute the foundation for creating guidelines compliant with the EBM. However, as the representation of the elderly population in clinical trials is too small because of reasons discussed above, it is not possible to draw important conclusions for this group of patients. Moreover, biological and physiological differences do not allow to apply the results of younger patients directly to the group of the elderly. Therefore, it is vital to include senior adults in ongoing trials preceded by a detailed and credible assessment of older patients' health status. It is equally or maybe even more important to design trials dedicated exclusively to seniors, taking into consideration functional, biological and social factors. A number of organisations conducting large scale cross-centre research have already begun to investigate this problem. The EU7 project entitled "Increasing the Participation of the Elderly In Clinical Trials" (PREDICT) investigated the reasons for the exclusion of senior adults from clinical trials not only in oncology but also in internal medicine and proposed solutions for this problems.<sup>28</sup>

Another example is work of the Elderly Task Force, which was created within the framework of the European Organisation for Research and Treatment of Cancer (EORTC). This group of specialists is responsible for developing methodology of conducting clinical trials with the participation of seniors. Tools recommended for screening health status of elderly patients have been suggested. They allow to categorise

patients into fit and frail as well as assess the functional reserves of an individual patient. The proposed set of instruments – Minimal Data Set (MinDS) – contains such tools as Instrumental Activities of Daily Living scale (IADL), G8, Charlson Comorbidity Index (CCI) and the evaluation of patient's social situation.

The recommendations also stress that besides the classic endpoints of a clinical trial, the emphasis should be put on assessing the influence of tested treatment on the quality of life (QoL), independence and functional status of seniors. Furthermore, a panel of experts recommended such collaboration with the pharmaceutical industry in which post-marketing studies would be obligatory for vulnerable older patients and suggested a detailed analysis of age groups in planned trials. Also, the International Society of Geriatrics (SIOG) in its plans for the nearest future stresses the significance of development of senior studies.<sup>29</sup>

## 6. Conclusions

It is necessary to widen the scale of phases I and II trials in the group of seniors with appropriate assessment of toxicity as well as to include larger groups of older patients in the phase III trials. This will allow a proper stratification and obtaining representative groups for statistical analysis and credible trial results. Another priority is the design of trials dedicated exclusively to the elderly.

The presented data suggest that the situation of older people diagnosed with cancer is improving and the awareness of the problem which we will soon face – be it as oncologists or as patients over 65 years of age – is growing.

## Conflict of interest

None declared.

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