

# The Challenges of Treating Cancer in Older Patients – How Effective Are Clinical Trials in Developing Unique Treatments?

a report by

Jacek P Grabowski,<sup>1,3</sup> Donatella Pintus,<sup>1</sup> Hodigere S J Ramesh,<sup>1</sup> Jacqueline Coyle<sup>1</sup> and Riccardo A Audisio<sup>1,2</sup>

1. Whiston Hospital, Prescot; 2. University of Liverpool; 3. Department of Oncology, Division of Gynecological Oncology, Poznan University of Medical Sciences

DOI: 10.17925/EOH.2008.04.1.94

Demographic changes in developing countries are leading to a rapid increase in the absolute number of the elderly population.<sup>1</sup> The management of elderly patients with cancer currently represents a major challenge for the medical community.<sup>2</sup> An elderly patient is arbitrarily defined as someone aged 65 years and over. It has been suggested that those aged over 65 should be divided into younger-old (age 65–74 years), mid-old (age 75–84 years) and old-old (age exceeding 85 years). The age of 75 years and older is usually set as the cut-off point for more vigilant attention, because the incidence of age-related physical changes increases sharply between 70 and 75 years.<sup>3</sup>

In industrialised countries, the fastest growing segment of the population is composed of individuals aged 65 years or over,<sup>4</sup> and this demographic group is predicted to increase by 13.3% by 2010 and by 53.2% by 2020.<sup>5</sup> The over-75-year-old group will triple by 2030, and the over-85-year-old group will double in the same period.<sup>6</sup> By 2050, 21% of the older population is expected to be aged 80 years or older.<sup>3</sup>

Over the last century, life expectancy has been steadily rising. In 2003, the US Vital Statistics estimated median life expectancy for 65-year-old men to be 17 years; for 70-year-olds it was 13 years, for 75-year-olds it was nine years and for 80-year-olds it was seven years.<sup>7</sup> This expansion in life expectancy, coupled with increased incidence of cancer, is having a profound effect on the prevalence of cancer.

The risk of developing cancer increases with ageing.<sup>1</sup> Over 50% of all new cancer cases are diagnosed in people aged 65 years or older, and over 60% of all cancer deaths occur in this group of the population.<sup>8</sup> Despite this, cancer diagnosis and treatment in the elderly has been under-researched, with elderly patients frequently being excluded from clinical trials.<sup>5</sup> Only a small subset of geriatric patients are being entered into clinical trials. Thus, elderly patients are still managed on the basis

of assumptions based on a younger population group.<sup>1</sup> Elderly patients with cancer should be assessed and treated differently from younger patients, as age-related physical changes affect the biology of cancer but also the physiology of elderly patients. These should be factored in while planning treatment.<sup>1,9,10</sup> Hence, older patients cannot be managed in the same way as their younger counterparts due to concomitant and possibly multiple medical problems.<sup>11</sup>

Ageing is a complex, heterogeneous and highly individualised process. A person's age alone does not always predict his or her physiological decline. This is due in part to the effect of co-morbidity on ageing.<sup>12</sup> Patients of the same chronological age can differ greatly in physiological age and other aspects of ageing.<sup>9</sup> Time of onset is affected by multiple factors including diet, race, sex, physical activity, habits and hormonal effect.<sup>1,26</sup> The hallmark of senescence is decreased functional reserve of individual organs and the reduced ability of these organs to cope with the challenge.<sup>1</sup> Ageing is associated with a decrease in gastrointestinal motility, splanchnic blood flow, secretion of digestive enzymes and mucosal atrophy, which can result in a reduced drug absorption rate.<sup>12–14</sup>

With age come changes in excretory function and a gradual loss in renal mass and clearance. Stem cell reserve appears to be compromised with ageing and may be responsible for increased haematological toxicity.<sup>12,15,16</sup> Changes in individual pharmacokinetics, pharmacodynamics and tolerance of normal tissues may influence the effectiveness and safety of cancer treatments in elderly patients.<sup>4,17</sup> Pharmacokinetic processes, such as the absorption, metabolism and excretion of drugs, appear to be different in older patients, and generally a person's physiological tolerance or reserve diminishes with increasing age.

The potential for drug interactions is relatively high in the elderly because of polypharmacy. Seventy-eight per cent of patients older than 65 years are on at least one prescribed medication, and 39% regularly take five or more drugs,<sup>18</sup> whereas up to 90% of elderly patients take over-the-counter drugs.<sup>19</sup> The majority of drugs prescribed to the elderly have been previously tested within randomised, controlled trials on a biologically different and much younger cohort.<sup>20</sup> It is important that pharmaceutical companies make an effort to develop drugs specifically for the elderly that are also tested on elderly patients.<sup>20</sup>

Older individuals with co-morbidities are also at risk of functional disabilities, which can impact on cancer treatment strategies. Age alone should never make a patient ineligible for a trial or other treatment, and the effects of ageing on bodily functions and physiology cannot be ignored when making treatment and referral decisions.<sup>21</sup>

Jacek P Grabowski is a Resident in Gynaecology and Obstetrics in the Department of Oncology, Division of Gynaecological Oncology at the Poznan University of Medical Sciences. He has a special interest in ovarian cancer diagnosis and treatment. In 2007 he was awarded a Fellowship at Whiston Hospital in Prescot by the European Society of Surgical Oncology (ESSO), where he worked with Mr Riccardo A Audisio. He is also working on his PhD thesis – 'Serum leptin levels and effectiveness of cytoreduction and chemotherapy in ovarian cancer patients – which he plans to finish in 2008.

E: jacek.grabowski@sk1.am.poznan.pl

Riccardo A Audisio is a Consultant in General Surgery/Oncology at Whiston Hospital in Prescot and has also been appointed Honorary Reader in the Department of Surgery. He has been exploring the role of surgery within the multidisciplinary management of cancer patients, particularly focusing on onco-geriatrics. Mr Audisio is a member of several scientific societies and sits on the National Committee of the British Association of Surgical Oncology (BASO). He is an active member of 12 Editorial Boards and is the Editor of *Surgical Oncology*.

The challenges of trials include ageist attitudes, personal beliefs, elderly beliefs, end-points of trials, practicality, feasibility, funding and publication related to the elderly. To provide evidence-based literature on the evaluation and management of elderly patients with cancer, clinical trials are needed to guide medical professionals in their decisions. This was recognised in 1989 when the US Food and Drug Administration (FDA) issued a recommendation that elderly patients should not be excluded from clinical trials.<sup>4,22</sup>

Despite this, the under-representation of elderly patients in cancer treatment trials is a persistent problem that is a result of scant elderly specific trials and unfair inclusion criteria favourable for younger

Omission of primary surgery in unselected elderly women with operable breast cancer who were fit for the procedure resulted in an increased rate of progression, therapeutic intervention and mortality.

patients. Without developing new trials designated especially for the elderly and improving their inclusion in the existing studies, it is difficult to determine how this population should be treated.

Fewer than 3% of newly diagnosed adult cancer patients participate in clinical trials, with the rate of elderly enrolment reaching only 25%.<sup>23-26</sup> The European Organisation for Research and Treatment of Cancer (EORTC) conducted an analysis of European trials in which 22% of the patients were aged 65 years or older and 8% were aged 70 years and older. The EORTC investigators, as well as others, advocate that the elderly should be candidates for all phases of clinical trials and that they should not be excluded on the basis of age.

There seems to be a need for a more comprehensive tool of pre-treatment assessment so that the potential problems in treating elderly patients can be predicted and avoided. Because ageing is the result of highly individualised processes, an assessment should be made of each patient to adequately plan therapy.<sup>6</sup> If we consider the low numbers of clinical trials dedicated to the elderly, and especially surgical trials, the effectiveness of these studies in the development of unique therapies for this group of patients seems to be very limited. It is important to identify the barriers to patient participation in clinical trials in order to reduce the disparity in the care of elderly cancer patients.

A literature review was undertaken to identify the barriers that impede the accrual of this vulnerable population into clinical trials and to determine what specific strategies are needed to improve the representation of older patients in research studies. The perceptions of physicians, protocol eligibility criteria with restrictions on co-morbid conditions and functional status to optimise treatment tolerability are the most important reasons resulting in the exclusion of older patients. Other barriers include the lack of social support and the need for extra time and resources to enrol these patients.<sup>27</sup>

Older patients are significantly under-represented in cancer clinical trials. Age is a significant barrier to recruitment; only one-quarter to one-third of potentially eligible older patients are enrolled into trials.<sup>28</sup> Most of the trial protocols limit the eligibility to participate on the basis of age, with the cut-off being between 65 and 70 years of age. This automatically excludes many patients on chronological age alone, without evaluating their health performance. The heterogeneity of this group of patients indicates the need to develop objective patient performance evaluation methods.<sup>5,28</sup>

Screening tests may become more accurate in older individuals because of the increased prevalence of cancer, but may be less beneficial as a result of more limited patient life expectancy. With more limited life expectancy, the effect of treatment on quality of life is paramount. Reliable assessment of quality of life is essential for interpreting clinical trials in older individuals. Today's older patient is much healthier and more active than in previous years. There is clearly a healthy subgroup of the elderly who can benefit from standard therapy. Because of the exclusion of patients with pre-existing diseases from clinical trials, few data are available on which to base optimal cancer treatment.<sup>29,30</sup> Current evidence suggests that the health of the oldest-old is improving and that interventions can still be successful even in more advanced age groups.<sup>31</sup>

Omission of primary surgery in unselected elderly women with operable breast cancer who were fit for the procedure resulted in an increased rate of progression, therapeutic intervention and mortality.<sup>32</sup> The reasons for not recommending surgery were protocol exclusion criteria affecting the elderly, many patient factors, treating clinician factors, lack of knowledge base and unfounded fear of adverse treatment outcome. In a recent study by O'Connell et al.,<sup>33</sup> among the

The reasons for not recommending surgery were protocol exclusion criteria affecting the elderly, many patient factors, treating clinician factors, lack of knowledge base and unfounded fear of adverse treatment outcome.

many reasons cited for not receiving cancer-directed surgery, "not recommended" achieved statistical significance. Rates of refusing surgery were <13.1% and contraindicated in <21.5%. Age was a strong predictor, beginning at 75-79 years, for which there was a steady increase in odds of surgery not being recommended. Hazard analyses showed that patients with all types of tumour who received cancer-directed surgery had a decreased hazard of dying.<sup>33</sup>

Clinician attitude and knowledge of the available ongoing clinical trials is the second most frequent factor related to patient enrolment.<sup>34</sup> Often, doctors do not check the current trials in order to find suitable treatments for elderly patients, resulting in very low inclusion. In addition, older patients are not included mainly because of their age and associated higher rate of co-morbidities, leading to clinician

unwillingness to enrol them. Although some women aged 70 years and over were included in trials, they tended to be selected because they were particularly healthy. Conversely, older patients do not view their age as an important reason for refusing trials.<sup>27</sup>

Clinical trials are constructed on the basis of an assumed homogeneous study group. This often does not apply to elderly patients because the population is very heterogeneous in health status and only the healthiest patients are included. Trials in older women are more difficult for a number of reasons related to their age, including the presence of other diseases, impaired physical status, depression and neurological impairment. Trials involving older women often require more time for their preparation and design as a result. However, if these trials are not conducted, we will discriminate against an already vulnerable group and deny ourselves vital information.

To encourage participation of elderly patients in clinical trials, innovative studies specifically designed for senior patients must be made available, while the use of a comprehensive geriatric assessment tool to determine the general health of patients rather than using chronological age should be encouraged. Study designs should be more inclusive of elderly patients, e.g. Post-operative Radiotherapy In Minimum risk Elderly (PRIME) and Endocrine ± Surgical Therapy for Elderly Women with Mammary cancer (ESTEEM), rather than using age as an exclusion criterion.

The health policies in most countries are in need of developing strategies to meet this growing problem. Changing the attitude of surgeons towards elderly patients with cancer comes with widening

our knowledge, as well as patient awareness of what positively influences patient enrolment.<sup>35</sup> It is the responsibility of today's doctors to train future generations to offer treatment on individual merits without age bias. Proactive participation of practising doctors and upcoming surgeons in ongoing national and international educational and scientific meetings should be encouraged.

The management of elderly cancer patients requires multidisciplinary skills: notably, close relationships between oncologists and geriatrics. Oncologists must assess patients' malignant disease and establish the diagnosis, staging and prognostic classification of tumours using comprehensive oncology assessment. Geriatricians must assess other aspects of their patients: cognitive and psychological domains, medical conditions, nutrition and functional status of the patient (comprehensive geriatric assessment).<sup>36</sup>

In conclusion, current inefficiency in the enrolment of elderly patients is based on many modifiable factors that have to be considered during the preparation of new clinical trial protocols. Development of trials designated especially for older patients should be based on a comprehensive geriatric assessment instead of metrical age limit.

Physicians should be encouraged to update their knowledge about ongoing clinical trials, together with increasing patient awareness on this subject. In addition, this constantly growing group of patients should be a stimulus for the pharmaceutical companies to place more interest in trials specific to the elderly. The comprehensive evaluation of these factors should improve elderly cancer patient enrolment and result in unique therapy development. ■

1. Ramesh HSJ, Pope D, Gennari D, Audisio RAA, Optimising surgical management of elderly cancer patients, *World J Surg Oncol*, 2005;3:17.
2. Terret C, Management and geriatric assessment of cancer in the elderly, *Expert Rev Anticancer Ther*, 2004;4:469–75.
3. Surbone A, Kagawa-Singer M, Terret C, Baider L, on behalf of the SIOG Task Force on Cultural Competence in the Elderly, *Ann Oncol*, 2007;18:633–8.
4. Townsley C, Pond GR, Pelozo B, et al., Analysis of treatment practices for elderly cancer patients in Ontario, Canada, *J Clin Oncol*, 2005;23:3802–10.
5. Pope D, Ramesh H, Gennari R, et al., Pre-operative Assessment of Cancer in the Elderly (PACE): a comprehensive assessment of underlying characteristics of elderly cancer patients prior to elective surgery, *Surgical Oncology*, 2007;15:189–97.
6. Lichtman M, Guidelines for the treatment of elderly cancer patients, *Journal of the Moffitt Cancer Center*, 2003;10:445–53.
7. Scardino PT, Surgery in elderly cancer patients, *Nat Clin Pract Neurol*, 2006;3:397.
8. Wedding U, Pientka L, Hoffken K, Quality-of-life in elderly patients with cancer: a short review, *Eur J Cancer*, 2007;43:2203.
9. Ershler WB, Cancer: a disease of the elderly, *J Support Oncol*, 2003;1(Suppl. 2):5–10.
10. Balducci L, Beghè C, Cancer and age in the USA, *Crit Rev Oncol Hematol*, 2001;37:137–45.
11. Terret C, A challenge for the future, *European Oncology Review*, 2005.
12. Lichtman SM, Treating elderly cancer patients: what you need to know about their physiology and specific medical needs, *Community Oncology*, 2006;3:730–34.
13. Yuen GJ, Altered pharmacokinetics in the elderly, *Clin Geriatr Med*, 1990;6:257–67.
14. Baker SD, Grochow LB, Pharmacology of cancer chemotherapy in the older person, *Clin Geriatr Med*, 1997;13:169–83.
15. Boggs DR, Patrene KR, Hematopoiesis and aging III: anemia and a blunted erythropoietic response to hemorrhage in aged mice, *Am J Hematol*, 1985;19:327–38.
16. Baraldi-Junkins CA, Beck AC, Rothstein G, Hematopoiesis and cytokines: relevance to cancer and aging, *Hematol Oncol Clin North Am*, 2000;14:45–61, viii.
17. Balducci L, Geriatric oncology, *Crit Rev Oncol Hematol*, 2003;46:211–20.
18. Jørgensen T, Johansson S, Kennerfalk A, et al., Prescription drug use diagnoses and healthcare utilization among the elderly, *Ann Pharmacother*, 2001;35:1004–9.
19. Hanlon JT, Fillenbaum GG, Ruby C, et al., Epidemiology of over-the-counter drug use in community dwelling elderly: United States perspective, *Drugs Aging* 2001;18:123–31 (Rieseman C, Antidepressant drug interactions and the cytochrome P450 system: a critical appraisal, *Pharmacotherapy*, 1995;15:84–99).
20. Repetto L, Audisio RA, Elderly patients have become the leading drug consumers: it's high time to properly evaluate new drugs within the real targeted population, *JCO*, 2006;24:e62–3.
21. Chalaire D, Participation of elderly patients in clinical trials: looking beyond age, *Oncology*, 2004;49.
22. Food and Drug Administration, Guideline for the study of drugs likely to be used in the elderly. Available at: [www.fda.gov/cder/guidance/old040fn.pdf](http://www.fda.gov/cder/guidance/old040fn.pdf)
23. Kaluzny A, Brawley O, Garson-Angert D, et al., Assuring access to state-of-the-art care for U.S. minority populations: the first 2 years of Minority-Based Community Clinical Oncology Program, *J Natl Cancer Inst*, 1993;85:1945–50.
24. Tejeda HA, Green SB, Trimble EL, et al., Representation of African-Americans, Hispanics, and whites in National Cancer Institute treatment trials, *J Natl Cancer Inst*, 1996;88:812–16.
25. Joseph R, Viewpoints and concerns of a clinical trial participant, *Cancer*, 1994;74:2692–3.
26. Hutchins LF, Unger JM, Crowley JJ, et al., Underrepresentation of patients 65 years of age or older in cancer-treatment trials, *N Engl J Med*, 1999;341:2061–7.
27. Townsley CA, Selby R, Siu LL, Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials, *J Clin Oncol*, 2005;23:3112–124.
28. Audisio RA, Pope D, Ramesh HS, et al., Shall we operate? Preoperative assessment in elderly cancer patients (PACE) can help, A SIOG surgical task force prospective study, *Crit Rev Oncol Hematol*, 2008;65:156–63.
29. Bayer A, Tadd W, Unjustified exclusion of elderly people from studies submitted to research ethics committee for approval: descriptive study, *BMJ*, 2000;321:992–3.
30. Bugeja G, Kumar A, Banerjee AK, Exclusion of elderly people from clinical research: a descriptive study of published reports, *BMJ*, 1997;315:1059.
31. Repetto L, Venturino A, Vercelli M, et al., Performance status and comorbidity in elderly cancer patients compared with young patients with neoplasia and elderly patients without neoplastic conditions, *Cancer*, 1998;82:760–65.
32. Fennessy M, Bates T, MacRae K, et al., Late follow-up of a randomized trial of surgery plus tamoxifen versus tamoxifen alone in women aged over 70 years with operable breast cancer, *Br J Surg*, 2004;91:699–704.
33. O'Connell JB, Maggard MA, Ko CY, Cancer-directed surgery for localized disease: decreased use in the elderly, *Ann Surg Oncol*, 2004;11:962–9.
34. Tournoux C, Katashian S, Chevret S, et al., Factors influencing inclusion of patients with malignancies in clinical trials: a review, *Cancer*, 2006;106:258–70.
35. Lara PN, Paterniti DA, Chiechi C, et al., Evaluation of factors affecting awareness of and willingness to participate in cancer clinical trials, *J Clin Oncol*, 2005; 23:9282–9.
36. Terret C, Zulian GB, Naiem A, et al., Multidisciplinary approach to the geriatric oncology patient, *J Clin Oncol*, 2007;25:1876–81.



**Göteborg, Sweden, 29 March – 1 April 2009**



## **Abstract Submission Deadlines**

**Wednesday, 26 November 2008**

**Tuesday, 16 December 2008**

**Nurses Group**

**Physicians & Data Management Group**

**[www.akm.ch/ebmt2009](http://www.akm.ch/ebmt2009)**

*Physicians Scientific Secretariat*  
Gunborg Bodö Aspström  
Section of Haematology and Coagulation  
Sahlgrenska University Hospital  
413 45 Göteborg / Sweden  
Tel. +46 (0)31 3428431  
Fax +46 (0)31 417438  
e-mail: EBMT2009@vgregion.se

*Organising Secretariat*  
EBMT 2009  
c/o AKM Congress Service  
Association House, P.O. Box  
4002 Basel / Switzerland  
Tel. +41 61 686 77 11  
Fax +41 61 686 77 88  
e-mail: ebmt@akm.ch