Under-representation of the elderly in cancer clinical trials

Cancer predominantly affects the elderly, but those over 65 years of age are significantly and consistently under-represented in clinical trials of potential new treatments. How important is this to cancer care in the elderly, are there identifiable reasons for the disparity and can anything be done to redress the imbalance?

We are in the midst of an unprecedented demographic revolution (Terret et al, 2007). Population trends across the world have resulted in increasing numbers of elderly patients. Older people now comprise the fastest growing section of the UK community (Crome, 2003). If current growth continues, in the next 50 years the proportion of the UK population aged 75 years and over will increase from 7% to around 11% with a disproportionate rise in those aged over 85 years (Turner et al, 1999). This population trend represents a major challenge to health-care provision, both clinically and economically.

Cancer is a disease of the elderly. Around 60% of new cancers and 70% of cancer-related deaths occur in patients over 65 years of age (Talarico et al, 2004). Improved understanding about the biology, treatment and clinical course of individual cancers shows that there are significant and unique biological characteristics to cancers in the elderly. Age remains a consistent adverse prognostic factor for attainment of remission and overall survival in most malignancies (Gondos et al, 2007).

However, despite this, the optimal cancer treatment for an older population is largely unknown because of the low numbers of elderly patients accrued onto clinical trials (Townsley et al, 2006). A retrospective analysis of trial data between 1997 and 2000 carried out by Talarico et al (2004) for the National Cancer Institute in the United States of America showed that over 65-year-olds represented only 32% of clinical trial populations in the USA even though they made up 61% of the American cancer population in the same period.

Cancer registries and trial demographics suggest similar huge discrepancies between cancer incidence in the elderly and the enrolment demographics of cutting edge cancer clinical trials. The clinical applicability of the results of a treatment trial depend to a large extent on whether the sample represents proportionally the entire spectrum of patients in clinical practice, therefore this under-representation suggests a potential uncertainty about the role of and benefits to elderly patients of any new treatment investigated this way and as such heralds a significant challenge to evidence-based practice (Kumar et al, 2007). Further, if those elderly patients who are included in trials are so chosen specifically for their good performance status and minimal co-morbidity then resulting data may have limited applicability to real world patients (Kohne et al, 2008).

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Scope of the problem

When Trimble et al (1994) compared the rates of cancer in people aged 65 years and older with their proportional representation in trials for the five most common malignancies in the United States they found striking differences. In men, overall trial population demographics reveal that 39% of participants were over 65 years old. With specific cancer subsets they found that 79.5% of prostate cancer trial patients were above this age but in leukaemia trials only 9.6% were over 65 years of age. In women, over 65-year-olds comprised 25.9% of the total trial population, the greatest proportion found in pancreatic cancer trials at 59.6%, although only 17.3% of breast cancer trial patients were over 65 years old. In general the discrepancies in representation of the elderly are most pronounced in leukaemia and cancers of the CNS, ovary and breast (Turner et al, 1999).

A systematic review by Kumar et al in 2007 looked at the demographics of patients recruited to phase III randomized trials conducted by American National Cancer Institute sponsored groups. The review found that of 345 randomized controlled trials for cancer treatment only fifteen had a population comprised of more than 40% aged over 65 years, while just seven had a population of more than 50% aged over 65 years. Significantly, the review also found that contrary to anecdotal reports of higher toxicity in the elderly, the same trials actually showed good outcomes of experimental therapy in older patients. Another review by Murthy et al (2004) found a strong relationship between enrolment fraction and age: in 30–64-year-olds, they showed a 3.0% enrolment fraction compared with only 0.5% in those over 75 years of age.

In the 1980s, various American studies revealed significant under-representation of women and African

Americans in clinical trials and as a result, their participation was legislated in 1989 and is now federally mandated by the US Food and Drug Administration (Hutchins et al, 1999; Townsley et al, 2005). No such mandate exists for the elderly.

What is the result of this lack of proportional representation in trials and is it significant? Repeatedly, analysis shows that patients enrolled onto clinical trials have better outcomes than those who are not (Gross et al, 2005). Pulte et al's (2008) review of the treatment of acute myeloid leukaemia in the elderly showed that in the past 20 years advances in survival of acute myeloid leukaemia extend to every age group except the elderly and that although evidence suggests that treatment can extend life expectancy in otherwise healthy patients, age was an important predictor of undertreatment.

These facts highlight a multitude of disparate points which suggest the multifactorial nature of the reasons behind low trial participation in elderly cancer patients. A number of studies, reviews and meta-analyses have tried to elucidate the reasons for this neglected area of clinical research and a multitude of factors have been postulated and explored. All may play a role.

Reasons for under-representation

Patient attitude

The decisions and opinions of patients and their families is a vital factor in any trial recruitment process. In younger cancer patients, Yee et al (2003) showed that the reasons given for trial participation included improved health, helping to find a cure for cancer and a desire for the most up-to-date treatment. Older patients stated the same reasons as their main drivers for participation although they also included the factor of undergoing the best available treatment.

In the elderly cancer patient, better quality of life was shown by Townsley et al (2006) to be perceived as more important than increased survival – however, one must remember that in such studies of patient attitude, those who respond to surveys are perhaps the individuals who are also more likely to participate in trials and therefore there may remain an unheard majority who have very different reasons for non-participation. The same study showed that most respondents would willingly consider participation in a clinical trial, but few are informed of the availability of trials nor do they actively seek them out.

French researchers Kohne et al (2008) asked patients aged between 70 and 95 years, both with and without cancer, in the USA and France to indicate their interest in undergoing intensive chemotherapy for cancer were it to be offered. Of the patients with cancer 77.8% of French respondents and 70.5% of Americans indicated a willingness to undergo the speculative therapy. In healthy respondents only 34% in France but 73.8% in the USA showed the same willingness. However, in both groups many who replied reported that they would be interested in chemotherapy even for small projected benefits.

Physician attitude

Hutchins et al's (1999) survey of American oncologists showed that 80% felt that trial patients had better outcomes. When patients are asked their reasons for trial participation, the attitude of their physician remains a major factor in the decision (Townsley et al, 2006).

However, despite this belief in better outcomes, Wright et al's (2004) American study showed that 51% of oncologists excluded patients from trials on the basis of age alone. Further studies have shown that when patient preference is taken over physician preference there is increased uptake of elderly enrolment (Turner et al, 1999).

Logistics

The elderly are more likely to suffer from a lack of financial, logistic and social support to facilitate their participation in clinical trials (Trimble et al, 1994). Distance to treatment centre is found to be a significant barrier to recruitment even though those who travelled further for treatment were more likely to survive (Gross et al, 2005).

These patient-specific factors are not easy to address given the economic constraints of trial protocols. But in order to recruit more elderly patients, the very fact that they are less likely to have relatives or friends able to help them reach trial centres must be recognized and efforts made to reduce inequality on the basis of access alone.

Comorbidity

Chronological age is not always predictive of physiological decline and the geriatric population comprises a heterogeneous group in whom the difference between the elderly and the frail elderly must be considered. All too often we homogenise the group when, in fact, great variation in health and wellbeing exist across a wide spectrum.

Nevertheless, comorbidity is a significant and common problem in elderly cancer patients and plays an important role in their treatment options. The typical elderly oncology patient will have three or more comorbidities (Gross et al, 2005) and in 2008 Girre et al reported that more than 50% of women older than 70 years treated for operable breast cancer died from causes other than their malignancy.

The high prevalence of depression and malnutrition in the elderly both predisposes to and is associated with an increased risk of functional decline and death, independent of other comorbidities and disease severity. Age-related cognitive decline also plays a vital role in recruitment as the ethics of enrolling a patient who does not have the capacity to consent to his/her own treatment, even in anticipation of a better outcome, is fraught with difficulties.

Despite the likelihood of comorbidities in the elderly patient, there is a spectrum of severity of comorbid disease and the otherwise fit elderly person with hypertension may tolerate intensive chemotherapy better than the elderly person with unstable angina. An assessment of the severity and impact of comorbid disease is required to ensure we do not inappropriately exclude otherwise fit patients from

potentially beneficial treatment options. The mechanism of how a given comorbidity leads to decreased survival in cancer patients is not understood: does it affect stage at diagnosis, choice of treatment, concordance with therapeutic regimens, treatment response or all points of the clinical trajectory of cancer care? Indeed, is it the cancer itself or the cancer's treatment that affects the comorbidity (Geraci et al, 2005)? More work is needed.

Toxicity

Historically, the first studies examining pharmacokinetics of drugs in older people were in hospitalized, frail patients. Age alone is not necessarily the most important determinant of altered pharmacokinetics; other factors include cigarette smoking, alcohol consumption, nutritional status, disease and frailty (Crome, 2003). The main alterations to pharmacodynamics with age are best described as changes in absorption (decreased gastrointestinal motility and blood flow), distribution (reduced volume of distribution as a result of decreased lean body mass and decreased body water), metabolism and elimination (increased elimination half life with age) (Bressler and Bahl, 2003). These all play a role in the potential for increased drug toxicity although exactly what that role is and its extent can only be assessed with age-specific trials in a wide variety of elderly people, both the fit and the unfit.

Where data exist, retrospective analysis of toxicity in chemotherapy trials shows similar rates between those less than 70 years old and the older patient. A retrospective chart review by Kohne et al (2008) showed fewer hospitalizations for toxicity in the elderly (16.5%) than those under 65 years of age (23.7%) although older patients did have more toxicity-related outpatient visits.

A research focus on elderly-unfriendly aggressive treatment may also contribute to poor recruitment numbers for some trials (Trimble et al, 1994).

Trial protocols

While exclusion criteria of clinical trials may not exactly specify age, many protocols indirectly exclude elderly patients in other ways that may subtly favour recruitment of younger patients. A review by Townsley et al (2005) found that around 90% of trials excluded individuals with previous cancer and more than 80% required patients to be ambulatory and capable of work or capable of all activities of daily living. The majority of cancer trials also exclude patients with haematological, hepatic, renal or cardiac abnormalities. Most literature agrees that chronological age is not a valid reason alone for trial exclusion (Siu, 2007) and there is currently no rigorous way to assess biological age (Yee et al, 2003).

Stringent eligibility criteria are necessary to guard against excessive treatment-related morbidity and mortality. At present higher morbidity and mortality is assumed on the basis of age alone, with the resultant situation that the true effect of trial agents can never be fully assessed in cancer patients who present with pre-existing comorbidities (Townsley et al, 2005). It can also be speculated that the stringent eligibility criteria of some trials are perceived as a proxy measure of potential toxicity by both patients and physicians.

Although they do exist, there are few elderly-specific cancer trials.

Discussion

Cancer is a disease whose treatment and biology has come to be better understood in the past 20 years through high powered, multicentre randomized controlled trials done across the world. This research focus has changed most cancers into a survivable disease, with remarkable advances notably in the areas of paediatric cancers and early stage colorectal malignancy (Kohne et al, 2008).

Despite this progress, and despite holding the dubious accolade of the population most likely to acquire a malignancy, the elderly have not enjoyed the same progress in survival and cure rates. This can be attributed to the interplay between host-related and disease-related factors but can also, to some extent, be apportioned to the continued under-representation of the elderly in cancer treatment trials which forces us only to speculate as to the exact nature of those host- and disease-related factors and how one might begin to treat them successfully. The result has been a paucity of truly representational evidence-based data for the treatment of malignancy in the elderly. We must take measures to address this in the next 20 years as over 65-year-olds from developed nations become the fastest growing sector of society.

The problems faced by the elderly cancer patient are by no means insubstantial. There are tentative efforts at present to introduce a more comprehensive geriatric oncology assessment with applicability of use in a busy oncology practice. This type of elderly-specific assessment would include quantifications of health, functional status, cognition and socioeconomic status, and psychological evaluation (Girre et al, 2008). No such validated tool yet exists but its use would be in defining the elderly less by their chronological age and more by the multifactorial aspects of their unique and diverse needs.

Specialties such as rheumatology, whose treatment decisions rely so heavily on subjective assessments of pain, function and disability, have adapted their practice and research focus in recent decades to devise and validate complex tools for both patient and physician reporting to provide composite measures of disease activity and inform treatment and monitor progress. Could such composite tools not be adopted into the oncologist's daily practice and adapted to provide a similar diagnostic, prognostic and objective tool?

Composite scoring tools could perhaps then be combined to provide a comprehensive geriatric assessment to aid both clinicians and patients in better and fuller documented assessment as to whether an individual patient is suitable for inclusion in clinical trials on the basis of both patient- and disease-specific factors and may go some

way to dispel the assumptive practice in place at present that age can be used as a proxy measure, predeterminant of poorer outcome. If trial coordinators are also involved in the development and validation of such composite scoring tools then more specific and inclusive protocols could be drawn up and may facilitate greater representation of the group who are most likely to benefit from the findings of such trials in the future.

There is no one answer to this problem although it seems clear that the area of support, be it financial, social or logistical, is one that the authors and sponsors of trial protocols are best placed to address. If we are to recruit and retain more elderly trial patients then we must be prepared for trial budgets to reflect the need to provide support in terms of transport to treatment centres, reimbursement of excess costs incurred and, in what could be an extended role to be placed within the purview of research nurses, personal support for those elderly patients with cancer who may have no other source of support in their community.

Another way to address difficulties in access to treatment centres would be for trial protocols to define a geographical area, rather than one or two specific hospitals, within which trial coordinators could recruit and then run satellite, community-based clinics to assess and deliver trial protocol treatments and follow ups. In this way, the disparity between survival in those who can travel further distances may be addressed; taking the best treatment to the neediest patients.

Trial protocols themselves are not without reproach, and it would be within the scope of trial design to consider less aggressive trial protocols with less rigorous exclusion criteria. At present, while age is not an acceptable or much used exempting reason for exclusion it can be the case that the elderly are indirectly excluded based on their current and previous medical history despite the fact that, in many cases, this would be unlikely to affect outcomes or fitness for experimental treatment. Could trial protocols be designed to include those patients who might otherwise have been excluded (e.g. those who have previously been treated curatively for unrelated malignancy) and take their results as a subset analysis? Might this be a first step to greater inclusion?

Conclusions

In the age of evidence-based medicine the inclusion of older patients in trials of cancer treatments is an area which needs urgent reassessment in order to offer patients truly excellent health care as we forge ahead into an era of greater longevity and greater scientific knowledge. **BJHM**

Conflict of interest: none.

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KEY POINTS

- Population trends mean we face a major expansion in the elderly patient group and therefore a greater cancer incidence.
- Sixty per cent of new cancers and 70% of cancer deaths occur in patients over 65 years of age.
- Evidence-based cancer treatment in the elderly is scanty as most trial populations comprise a third or less elderly people and are not truly representative of the population they serve.
- Age is an important predictor of under-treatment in cancer patients.
- There is no good evidence for worse toxicity or poorer outcome in elderly cancer patients enrolled onto trials.
- Trial protocols often too strictly exclude co-morbid disease in participants but this is neither representative of the target group nor evidence based.
- More work must be done to provide comprehensive geriatric assessment to address biological, psychological, social and economic barriers to trial recruitment and participation in the elderly.