Adjuvant chemotherapy in the elderly

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Cancer is predominantly a disease of the elderly: approximately 60% of all tumors and two-thirds of cancer-related deaths occur in those over 65 years of age. This proportion will grow with the expected increase in the size of the older population in the coming decades. For example, if incidence rates remain constant, the number of elderly women diagnosed with breast cancer in the US will increase by 72% by 2025 [1].

Adequate directives for the treatment of this important group of patients are often lacking, because the elderly have generally been excluded from clinical trials. In an analysis of European Organisation for Research and Treatment of Cancer (EORTC) phase II enrollment, only 22% of patients were ≥65 years of age and 8% were ≥70 years of age; a later Eastern Cooperative Oncology Group (ECOG) trial enrollment report stated that from 1998 to 1999, about 35% of trial participants were ≥60 years of age and only about 17% were ≥70 years of age [2, 3]. Possible reasons for poor participation include the following: few trials are specifically designed for elderly patients; physicians, patients and family members may think that older patients are less likely to benefit from and are less able to tolerate appropriately intensive treatment; the elderly may be less aware of medical developments and less likely to seek out clinical trials; older people are more likely to have other health problems (co-morbidities); and there is lack of financial, logistic and social support for participation of older patients in trials.

There is substantial evidence to indicate that, with a range of tumor types, elderly patients have a relative survival similar to that of younger patients when given comparable treatments [4–6]. However, a number of studies have shown that elderly patients often have more advanced disease at the time of diagnosis and receive fewer intensive treatments [7–12]. There is therefore concern that elderly patients frequently receive inadequate treatment. It should be noted, however, that other competing causes of mortality assume a large role in determining survival in older patients and that, relative to other causes of death, breast cancer mortality decreases as patients age [13–15]. In sum, the issues of major concern for evaluating an elderly patient with cancer are whether the patient will die with cancer or of cancer, and whether treatment will produce more benefit than harm.

Which patients should receive adjuvant chemotherapy?

Ageing is associated with a progressive decline in the functional reserve of multiple organ systems. In turn, this is responsible for an increased prevalence of co-morbidities and functional depend-
Treatment options: what do we know from clinical trials and what do we do in clinical practice?

Breast cancer

The Oxford Overview has shown that polychemotherapy induces a highly significant benefit in terms of relapse and survival rates up to 70 years of age, even if this seems to decrease with increasing age [22]. Unfortunately, only 600 women ≥70 years of age (0.03%) were included in the 47 adjuvant chemotherapy trials analyzed, rendering it impossible to determine the benefit of chemotherapy in this age group.

The French Adjuvant Study Group (FASG) recently presented the results of a randomized trial in which 338 node-positive breast cancer patients >65 years of age were treated with either tamoxifen 30 mg/day for 3 years (n = 164), or epirubicin 30 mg on days 1, 8 and 15 every 4 weeks for six cycles, plus tamoxifen as in the hormonal arm (T-E, n = 174) [23]. The primary study endpoint was disease-free survival (DFS). The median age was 69 years in both arms. The median PS was not given, but according to the study’s inclusion criteria, World Health Organization PS had to be less than two. A univariate analysis showed no differences in terms of time to relapse and survival between the two treatment arms. The results of a multivariate analysis indicated that 6-year DFS was significantly longer in the T-E arm (P = 0.007), with no differences found between women younger or older than 70 years of age. With the schedule indicated, single-agent epirubicin was well tolerated and feasible for women >65 years of age. Thus, the FASG trial has the merit of being the first study to evaluate the additive value of chemotherapy to hormonotherapy in elderly patients with early breast cancer. However, it should be noted that 13% of the patient population had negative hormone receptors, and tamoxifen was given for a suboptimal treatment duration.

A questionnaire was recently circulated among members of the Breast International Group (BIG) with the aim of collecting information about their personal experience and opinions regarding the management of elderly patients with early breast cancer [24]. BIG is a consortium of over 30 academic cooperative groups based in Europe, Australia–New Zealand, South America and Canada that have affiliated centers around the world. Some of the issues investigated include the chronological definition of ‘elderly’; the criteria used to define an elderly patient as a candidate for adjuvant chemotherapy and the age limit for offering such therapy; the use of geriatric assessments; the definition of the most interesting/acceptable treatment options and chemotherapy regimens; and the most realistic study end points for adjuvant chemotherapy trials in this age group.

The following data emerged from the 277 oncologists who participated in this survey. There was general agreement that if chronological age is used as a frame of reference to define the elderly population, 70 years of age represents the appropriate landmark. Forty-three per cent of the participants in the survey believed that there is no age limit for adjuvant chemotherapy, and <30% consider solely a patient’s chronological age as a criterion for proposing adjuvant chemotherapy. Cyclophosphamide, methotrexate and 5-fluorouracil (CMF) days 1 and 8 every 4 weeks for six cycles is the most commonly used regimen in the countries represented, with the exception of Australia, where a preference for anthracycline-based regimens was indicated, and the UK, where 3 weekly CMF was most common. Almost no collaboration exists between oncologists and geriatricians, and a geriatric assessment is rarely performed before proposing adjuvant treatment.

Colon cancer

Sargent et al. [25] performed a pooled analysis of data from seven randomized phase III trials (n = 3351 patients) in which the effects of postoperative fluorouracil (5-FU) plus leucovorin (five trials) or plus levamisole (two trials) were compared with the effects of surgery alone in patients with stage II or III colon cancer. The patients were grouped into four age categories: <50, 51–60, 61–70 and >70 years. No significant interaction was observed between age and the efficacy and safety of treatment. However, the authors underline how “the principal limitation of this study concerns its potential applicability to the general population of elderly patients. As a result of exclusion criteria and screening, elderly patients who enter clinical trials are a selected group, with good performance status and cognition, and limited numbers of coexisting conditions”. Therefore, the conclusions of these trials cannot be extended to the elderly colon cancer population in general.

Iwashyna and Lamont [26] performed a population-based cohort study of 3357 elderly Medicare beneficiaries who had undergone resection of stage III colon cancer according to the Surveillance, Epidemiology and End-Results registries to evaluate the effectiveness of adjuvant 5-FU in clinical practice. The authors used propensity score matching to compare the all-cause mortality of patients who received 5-FU to matched untreated patients. The results showed a clear survival benefit associated with 5-FU, and this effect does not diminish with advancing patient age. Nevertheless, the authors acknowledge that “there are limitations to the work”, mainly methodological.

Treatment options: the future

Prospective randomized clinical trials targeting elderly patients are definitively needed to understand the role of adjuvant chemotherapy in this group of patients. No standard chemotherapy regimens exist for elderly breast cancer patients, and there is concern about whether regimens that are commonly used in the younger population, i.e. those that are CMF-based or anthracycline-containing, represent ideal treatment options in the elderly. In particular, a significant relationship between age and a higher incidence of grade 3 toxicity from chemotherapy was observed among postmenopausal ER-positive patients who were randomized between tamoxifen and tamoxifen plus three cycles of classic CMF in the International Breast Cancer Study Group trial VII [27]. New drugs and new treatment schedules with low toxicity profiles, i.e. capcitabine, liposomal doxorubicin, vinorelbine and weekly taxanes, are interesting options to be explored in this domain. Recently, a phase III trial targeting women aged ≥65 years who present with a carcinoma of the breast >3 cm or with positive axillary nodes was activated in the USA and Canada. The patients are randomized to polychemotherapy consisting of four cycles of doxorubicin–cyclopophamide or six cycles of classic
CMF in cases of impaired cardiac function or to six cycles of single-agent capecitabine given at the dose of 1000 mg/m² twice daily for 14 consecutive days every 3 weeks. The lack of a no chemotherapy control arm is quite remarkable.

Adjuvant chemotherapy trials are also being discussed within other cooperative groups such as those represented by BIG. The survey conducted among its members showed that both the presence of a no chemotherapy arm and the investigation of a treatment option that is potentially less toxic and possibly as effective as polychemotherapy, i.e. single-agent chemotherapy, are considered relevant by oncologists in the BIG network [24]. Only 2% of the participants surveyed would be interested in exposing healthy elderly patients to the risk of a potentially more toxic and more effective regimen than 'standard' polychemotherapy. Interesting concepts such as the evaluation of low-dose chemotherapy given as anti-angiogenic therapy are under discussion.

The standard adjuvant treatment for patients with colon cancer in the UK consists of weekly 5-FU and low-dose folinic acid for 30 weeks. Open questions are whether elderly patients could benefit from shorter treatment duration and an oral drug. The Medical Research Council is planning to address these questions in a future randomized trial targeting patients ≥65 years of age.

Conclusion

The ageing of the population, a major and unexpected epidemiological event of the second half of the 20th century, represents a major challenge for medical practice. Elderly patients with cancer have usually been excluded from adjuvant chemotherapy trials. Medical oncologists are confronted every day with elderly patients who could ‘theoretically’ benefit from an adjuvant treatment, but find themselves in a position where it is impossible to practice evidence-based medicine with this population. Data are emerging for a subset of fit patients that will justify the evaluation of adjuvant chemotherapy, and ongoing/planned clinical trials will address the role of adjuvant chemotherapy in this subgroup of healthy older patients. Progress in the treatment of elderly cancer patients who have several and/or serious co-morbidities is slow in coming. This will represent a major challenge in the next decade.

References