Adjuvant Chemotherapy for Elderly Women with Breast Cancer:
Immediate Benefit and Long-Term Risk

Matti S. Aapro, M.D.
IMO Clinique de Genolier
Switzerland
Management of breast cancer in elderly individuals: recommendations of the International Society of Geriatric Oncology


Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer mortality in women worldwide. Elderly individuals make up a large part of the breast cancer population, and there are important specific...
BACKGROUND MESSAGE

COMORBIDITIES and concomittant treatment modulate strategies for non MBC
Life expectancy in senior adults: a large variability reflecting health status variability

Adjuvant Therapy in the Elderly: Making the Right Decision

Hyman B. Muss, Laura Biganzoli, Daniel J. Sargent, and Matti Aapro

ABSTRACT

Adjuvant chemotherapy has led to improvements in relapse-free and overall survival in patients with breast, colon, and non-small-cell lung cancer, yet many older patients are not offered these potentially life-saving treatments. Moreover, older patients have been either excluded or underrepresented in most adjuvant trials, limiting the generalizability of these treatments to older populations. Limited data in elders suggest that older patients derive significant benefits from adjuvant therapies provided they have life expectancies exceeding 5 years. Making treatment decisions in elders is challenging. Many have major comorbidities that may substantially limit life expectancy and minimize or negate the benefits of adjuvant chemotherapy. In this review, we discuss the potential benefits of adjuvant treatment in older patients with solid tumors with a focus on general principles involved in the selection of adjuvant therapy for patients with breast, colon, and non-small-cell lung cancer. In addition, we discuss the role of comorbidity and how it factors in treatment decisions. Finally, we discuss future research directions and funding for elders with cancer.

BUT COMORBIDITIES should not be a reason to forget clinical data and tumour biology
Breast Cancer in the Elderly

Diana Crivellari, M. Aapro, Robert Leonard, Gunter von Minckwitz, Etienne Brain, Aron Goldhirsch, Andrea Veronesi, and Hyman Muss

Abstract

Screening and adjuvant postoperative therapies have increased survival among women with breast cancer. These tools are seldom applied in elderly patients, although the usually reported incidence of breast cancer is close to 50% in women 65 years or older, reaching 47% after 70 years in the updated Surveillance, Epidemiology, and End Results (SEER) database. Elderly breast cancer patients, even if in good medical health, were frequently excluded from adjuvant clinical trials. Women age 70 years who are fit actually have a median life expectancy of 15.5 years, i.e., half of them will live much longer and will remain exposed for enough time to the potentially preventable risks of a relapse and specific death. In the last few years, a new concern about this issue has developed. Treatment now faces two major end points, as in younger women: to improve disease-free survival in the early stages, and to palliate symptoms in advanced disease. However, in both settings, the absolute benefit of treatment is critical because protecting quality of life and all its related aspects (especially functional status and independence), is crucial in older persons who have more limited life expectancy. Furthermore, the new hormonal compounds (aromatase inhibitors) and chemotherapeutic drugs (capecitabine, liposomal doxorubicin), are potentially less toxic than and equally as effective as older more established therapies. These new treatments bring new challenges including higher cost, and defining their benefit in elderly breast cancer must include an analysis of the cost/benefit ratio. These issues emphasize the urgent need to develop and support clinical trials for this older population of breast cancer patients both in the adjuvant and metastatic settings, a move that will take us from a prejudiced, age-based medicine to an evidence-based medicine.

J Clin Oncol 25:1882-1890. © 2007 by American Society of Clinical Oncology
ELDERLY AND BREAST CANCER

Presents at a more advanced stage

BUT
lower rates of tumour cell proliferation,
a lower expression HER2
a higher content of ER and PgR
a higher frequency of diploidy
a lower frequency of p53 accumulation

AND!
20% to 30% of older patients

poor/negative ER and PgR expression
UNDERTREATMENT

• 407 women > 80 years old

• 50% undertreated
  – *No surgery or tumorectomy without radiation*

• Reasons
  – *Refusal (patients) : 14%*
  – *Physician or family decided…*

• 5 year survival
  – «*State of the art » : 90%*
  – *lesser therapy : 46%*

*Bouchardy, JCO 2003*
WILL an « ELDERLY » ACCEPT CHEMOTHERAPY?

- 320 outpatients (France / USA) aged 70 years to 95 years (29% aged 80 years and older)
- With and without cancer
- Interviewed via anonymous questionnaires

- French noncancer patients (34%) were less willing to accept the strong chemotherapy than French cancer patients (77.8%), American noncancer patients (73.8%), and American cancer patients (70.5%) (P < .001 for each pair).

- This was also true for the moderate chemotherapy (67.9% v 100%, 95.2%, and 88.5%, respectively; P < .001).

Which schedule?  
Any benefit?  
... in the elderly  

Courtesy of  
A. Benavides
Which adj regimens for BrCa in the elderly

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Score</th>
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<tr>
<td>CMF 1,8 (6 cycles)</td>
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<tr>
<td>CMF 1,8 (3 cycles) *</td>
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<tr>
<td>A-based regimen (4 cycles)</td>
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<tr>
<td>A-based regimen (6 cycles)</td>
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<tr>
<td>3 weekly CMF</td>
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</tr>
<tr>
<td>Personalized regimens</td>
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</tbody>
</table>

Score : 0= 0%; 10= 100% investigators


*IBCSG trial VII: TAM vs CMF x 3 → TAM (Anthra: FASG-08; ICCG)

(↑grade 3 tox in 65+)

Crivellari et al. JCO 2002
Patients aged 65 years and older derive similar proportional improvement in relapse-free and overall survival as younger patients, but with a higher rate of treatment-related mortality.

Further evidence for Adj chemo in elderly patients

SEER database

Adjuvant chemotherapy: 15% relative reduction in mortality among women aged 66 and over with hormone receptor-negative breast cancer (adjusted hazard ratio 0.85, 95% CI 0.77-0.95)

Elkin EG, Hurria A, Mitra N et al.
J Clin Oncol 2006;24:2757-2764
Late complications of adjuvant chemotherapy

- Clinically significant congestive heart failure develops in 0.5 to 1.0 percent of women treated with standard anthracycline-based chemotherapy regimens.

- Risk factors for cardiac toxicity include older age, preexisting cardiac disease, higher cumulative dose of anthracycline, and irradiation of the

- Myelodysplastic syndromes or acute myeloid leukemia can arise as a consequence of chemotherapy. The risk is very low (0.2 to 1.0 percent) after standard chemotherapy with cyclophosphamide, methotrexate, and fluorouracil or anthracycline-based adjuvant chemotherapy

Burstein HJ, Winer EP

More on cardiotoxicity

SEER Database
Women aged 66 to 70 years (but not in 71-80 yr cohort!)
Hazard ratio (HR) for CHF due to adjuvant anthracyclines
(compared with other chemotherapy): 1.26 (95% CI 1.12-1.42)

AT 10 YEARS: 38% of anthracycline-treated women had CHF vs 33% with non-anthracycline chemotherapy and 29% among those who had had no adjuvant chemotherapy.

International Society of Geriatric Oncology Chemotherapy Taskforce: Evaluation of Chemotherapy in Older Patients—An Analysis of the Medical Literature

Stuart M. Lichtman, Hans Wildiers, Etienne Chatelut, Christopher Steer, Daniel Budman, Vicki A. Morrison, Brigitte Tranchant, Iuliana Shapiro, and Matti Aapro

ABSTRACT

The elderly comprise the majority of patients with cancer and are the recipients of the greatest amount of chemotherapy. Unfortunately, there is a lack of data to make evidence-based decisions with regard to chemotherapy. This is due to the minimal participation of older patients in clinical trials and that trials have not systematically evaluated chemotherapy. This article reviews the available information with regard to chemotherapy and aging provided by a task force of the International Society of Geriatric Oncology (SIGO). Due to the lack of prospective data, the conclusions and recommendations made are a consensus of the participants. Extrapolation of data from younger to older patients is necessary, particularly to those patients older than 80 years, for which data is almost entirely lacking. The classes of drugs reviewed include alkylators, antimetabolites, anthracyclines, taxanes, camptothecins, and epipodophyllotoxins. Clinical trials need to incorporate an analysis of chemotherapy in terms of the pharmacokinetic and pharmacodynamic effects of aging. In addition, data already accumulated need to be reanalyzed by age to aid in the management of the older cancer patient.

J Clin Oncol 25:1832-1843. © 2007 by American Society of Clinical Oncology
Combination chemotherapy vs capecitabine in ESBC patients > 65 years: improved outcomes

- Primary end point: relapse-free survival
- Results:
  - 2 toxic deaths with capecitabine
  - Significant improvement in DFS and OS with CMF/AC

Muss HB et al. ASCO 2008; Abstract 507.
THE BIOLOGICAL REALITY

BUT WHAT ABOUT ER+ PATIENTS WITH HIGH Ki-67?
NO, I DID NOT FORGET HER-2!

Arnd Hönig earlier today....
T*C vs AC USO 9735
Overall survival by treatment and age group

Hematologic and late cardiac toxicity by treatment and age (USO 9735)

Grade 3/4 hematologic toxicities (%)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>&lt; 65 years</th>
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<th>≥ 65 years</th>
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<td>AC (N=428)</td>
<td>TC (N=78)</td>
<td>AC (N=82)</td>
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<tr>
<td>Febrile neutropenia</td>
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<td>8</td>
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</tr>
</tbody>
</table>

3 MDS/leukemias and 1 death due to CHF in the AC arm

Position Paper

EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours

M.S. Aapro\textsuperscript{a,*,m}, D.A. Cameron\textsuperscript{b,η}, R. Pettengell\textsuperscript{c,ο}, J. Bohlius\textsuperscript{d,p}, J. Crawford\textsuperscript{e,q}, M. Ellis\textsuperscript{f,r}, N. Kearney\textsuperscript{g,s}, G.H. Lyman\textsuperscript{h,t}, V.C. Tjan-Heijnen\textsuperscript{i,u}, J. Walewski\textsuperscript{j,v}, D.C. Weber\textsuperscript{k,w}, C. Zielinski\textsuperscript{l,x}, European Organisation for Research and Treatment of Cancer (EORTC) Granulocyte Colony-Stimulating Factor (G-CSF) Guidelines Working Party
Breast adjuvant trials for older patients

GERMANY: “ICE”

Ibandronate 50 mg p.o. daily for 2 years or Ibandronate 6 mg i.v. every 4 weeks for 2 years

The decision of oral or intravenous application will be up to the patient.

No cytotoxic treatment

Capecitabine 1000mg/m² bid PO, days 1–14 every 3 weeks/5 cycles
ICE at ESMO ECCO 09

1409 pts
Median age 71 years (range 64–88)
570 (80.7%) HR + and 133 (19.3%) HR -
335 (48.2%) LN + and 368 (51.8%) LN -

305 SAEs: gastrointestinal (45), skin (38) and cardiac (43) disorders

T. Reimer et al
European Journal of Cancer Supplements
Vol 7 No 2, September 2009, Page 215
MANY ELDERLY PATIENTS BENEFIT FROM ADJUVANT CHEMOTHERAPY FOR BREAST CANCER

but doxorubicin might not be the best choice!
THANK YOU

to all the patients

and their

physicians, nurses and carers