To complicate further the interpretation there was no correlation between comorbidity and performance status (Table 1).

Table 1. Correlation between comorbidity and performance status

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Performance status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0+1</td>
</tr>
<tr>
<td>Significant</td>
<td>11*</td>
</tr>
<tr>
<td>Not significant or absent</td>
<td>13*</td>
</tr>
</tbody>
</table>

*Number of patients

Eleven patients had significant comorbidity but, due to successful symptomatic treatment, performance status was 0+1; 11 patients had both significant comorbidity and performance status 2 or 3; 12 patients had no significant comorbidity but performance status 2 or 3, which was therefore, lymphoma related. That leaves only 13/47 patients with both performance status 0 or 1 and no significant comorbidity.

That practically means that only 25% of elderly high-grade lymphoma patients can fulfill classical criteria to be included in a chemotherapy clinical trial. Comorbid situations, previously well compensated, tend to deteriorate irrespective of adequate treatment; deterioration might be due either to lymphoma or to chemotherapy or both. Therefore, clinical trials with elderly patients with aggressive non-Hodgkin's lymphoma with performance status 0 or 1 and no serious coexisting disease as inclusion criteria, target only to a minor prognostically better subgroup among these patients and can not be extrapolated to elderly patients with non-Hodgkin's lymphoma in general.

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Breast cancer in elderly patients

KEYWORDS: Lymphoma, Non-Hodgkin; Antineoplastic Agents; Aged

Age is a major risk factor for breast cancer. More than 50% of breast cancer occur in women 65 years of age and older. The increasing incidence of breast cancer with age has been seen predominantly in women older than 50 years (peak in 80 years, plateau between 80 and 85 years of age). According to cancer statistics, 1 in 15 women aged 60-79 years developed breast cancer compared to 1 in 25 women aged 40-59 years and 1 in 272 women younger than age 39 years (1).

With increasing age, the risk of co morbid conditions and cancer-related death also increase. As many as 50% of women 65 years of age and older who develop breast cancer die of the disease (2). Breast cancer in elderly population is presented with some specific characteristics with direct consequences on the therapeutic approach:

- They are frequently diagnosed at more advanced stage and most of them are metastatic at the time of diagnosis versus 5% in younger women.
- More indolent course of breast cancer with high prevalence of positive hormonal receptors, well-differentiated and slowly proliferating tumors.
- Higher comorbidity rate.
- Progressive declines of functional reserve of multiple organs with age.
- Poor financial and social background.
- Limited access to transport.

The multidisciplinary approach to this cancer includes prevention, early detection, treatment of localized tumors and management of advanced disease. Decisions related either to prevention or treatment need to be individualized, by weighing the probable benefits of treatment against the potential risk. Because aging is highly individualized, the best guide to breast cancer treatment in the elderly (3) may be provide by comprehensive geriatric assessment (CGA) which takes into account:

- Assessment of comorbidity
- Assessment of socioeconomic conditions
- Assessment of functional dependence
- Assessment of emotional and cognitive conditions
- Life expectancy

**BREAST CANCER PREVENTION IN THE ELDERLY**

Chemoprevention with estrogen antagonists is the most promising form of primary breast cancer prevention in older women. In the recent NSABP P-
1 trial (tamoxifen versus placebo) which included all "high risk" women aged 60 years or older, there was nearly a 50% reduction in the incidence of invasive and noninvasive breast cancer after median follow up of 69 months (4). In this trial 30% of participants were older than 60 years, and 6% were older than 70 years. Balanced against this benefit was the risk of toxicities such as deep vein thrombosis, pulmonary embolism and endometrial cancer. New antiestrogens (SERMs), such as raloxifene, could be attractive and may improve the risk to benefit ratio. NSABP P-2 (tamoxifen versus raloxifene) trial is underway.

Secondary prevention through the screening of asymptomatic women is the most established form of breast cancer prevention. Large randomized trials have shown that routine annual or biannual mammography in women aged 50-75 years is associated with reduction in breast cancer-related mortality of 25% to 30% within 5 to 6 years of initiation (5). Aging may affect screening results. The benefits of screening mammography are first seen three to seven years after initial mammography. Thus, screening mammography is not useful when life expectancy would be less than five years (6). At an older age, any specific screening strategies should become more individualized and based of life expectancy (i.e. the presence of comorbidity).

**MANAGEMENT OF EARLY BREAST CANCER**

Standard versus nonstandard treatment: Standard treatment of early breast cancer consider the integration of local and systemic treatment by use of curative surgery (radical mastectomy or quadrantectomy plus axillary lymph node dissection), radiotherapy and systemic therapy (hormonal or chemotheraphy). Advanced aged is found to be a risk factor for under-treatment, even after control comorbidity, cognitive status, social support and functional status (7). Older women are less frequently treated by surgery (8) and also have less extensive surgical procedures and less adjuvant radiotherapy; as a result of under-treatment, a decrease of ten years disease-related survival was seen in older women compared with younger patients -32% versus 57% (10). Other authors have documented omission of adjuvant radiation after breast conservation and less breast-preserving procedures in older women (8,9).

The main factor affecting surgical morbidity in older women in not age but the presence of comorbidity (8,10). They tolerate breast surgery well, with only 1% to 2% of operative mortality. Even women aged 70 years and older prefer breast conserving surgery than mastectomy (11). Merchant and Solin find that standard treatment of breast cancer has similar outcomes in older and younger women (12,13), but the older women had more deaths from intercurrent disease (p<0.05).

The 1998 updated meta-analysis of adjuvant therapy (16) show the benefit of adjuvant tamoxifen therapy and adjuvant chemotherapy in improving relapse-free and overall survival in women with early breast cancer. Tamoxifen therapy offers marked benefit to women with estrogen receptor positive tumors, as did to women with unrecorded receptor status, as well to postmenopausal women including those older than age 70 years.

Compared with tamoxifen, less is known about the impact of adjuvant chemotherapy on disease-free and overall survival in elderly patients. In the Oxford overview, only approximately 600 women (3%) were 70 years and older (17), and this sample size was insufficient to determine the value of adjuvant chemotherapy in this age group. For patients aged 50-69 years, the mortality reduction translates into 2% and 3% net gains in 10-years survival. Anthracycline-containing regimens was associated with a small, but significant reduction in the risk of recurrence and with a marginal reduction in mortality compared with standard CMF chemotherapy. Non-anthracycline containing regimens might be preferable, because advanced age is associated with more pronounced doxorubicin-induced cardiomyopathy. Another possibility for older women might be the use of milder regiments as MF/L (metotrexat and 5-fluoururacil with leucovorin).

The availability of newer agents also poses a challenge for the adjuvant treatment of the elderly (capecitabin, docetaxel, paclitaxel, and trastuzumab). In elderly women two adjuvant trials with capecitabin are undergo (capecitabin versus control and capecitabin versus FEC chemotherapy).

Nonstandard management. Tamoxifen as a first line treatment instead of surgery for operable breast cancer is therapy of choice in older patients who are unable to tolerate surgery or refused surgery. Despite high response rates of 30% to 60% most patients experienced relapse during tamoxifen therapy alone (more than 60%) requiring further local therapy-surgery or radiotherapy. Surgery results in better local control.

A recent meta-analysis of two large European trials (GRETA and CRC) evaluated the benefits of tamoxifen alone versus the combination of curative surgery with tamoxifen (14). These studies each randomized a total 406 and 447 patients, median age 76 years. After median five-year follow up, one study found that women 70 to 73 years of age had 33% reduction in risk of death following surgery plus tamoxifen compared with tamoxifen alone. But, women older than 73 years did not gain significantly in overall survival. These findings suggest that we can identify some frail patients who may not benefit from surgery.

Other non-standard combinations of tumor excisions, tamoxifen and radiotherapy result in better local tumor control and may improve survival. Retrospective data of the use of tamoxifen alone after lumpectomy rise skepticism, because local recurrence rates may be higher without radiation (15).

The role of axillary lymph node dissection in older women is another field of controversy, because small retrospective reports suggested that this procedure might be avoided and replaced with sentinel node biopsy, which is associated with minimal morbidity and is helpful for assessing nodal status of patients.

**MANAGEMENT OF METASTATIC BREAST CANCER**

Metastatic breast cancer is incurable and requires systemic treatment. The treatment is palliative in nature and should be focused on maintaining the quality of life. Endocrine manipulation is the cornerstone of therapeutic strategy in metastatic breast cancer in elderly, because steroid receptors are positive in over 60% of cases. Response rate is directly correlated to hormone receptor status. If the status is unknown, a RR of 30-35% is observed, while ER+ has a response rate of 45-50% and ER+ and PR+ show rates of 55-60% (NIH Consensus 1980). In the event of unknown receptor status, it is adequate to start treatment with hormonal therapy if there are a long disease interval, non-visceral metastases in bone, lymph nodes or cutaneous metastases or response to prior endocrine therapy.

The specific activity of tamoxifen in elderly patients has been examined. An analysis of four prospective trials (n=396), suggest that among patients older the age 65 years tamoxifen was superior than in younger women in terms of time to progression and overall survival (18). In other study, tamoxifen yields higher RR (45% vs. 33%) and longer duration of response (10.4 vs. 7.9 months) when compared with CMF in patients older than then age of 65 years (19). In addition to tamoxifen, nonsteroidal or steroidal aromatase inhibitors, as well as megestrol acetate and medroxyprogesterone acetate (proggestational agents) are available for therapeutic use.

In the absence of response to hormonotherapy at any stage, chemotherapy is indicated, as well as in the presence of life-threatening metastases.

With few exceptions, chemotherapy use in the elderly should be little different from the use in younger patients. Conventional regiments appear to be active in the elderly as in younger patients. Case comparative studies (20) showed that women aged 70 years and older had response rates to multidrug chemotherapy similar to those for women aged 50-69 years and women younger than 50 years (RR: 29%, 31% and 40% respectively, p=0.53). Toxicity profiles of the standard chemotherapy regimens for metastatic breast cancer are similar in younger and older women who are in reasonable general health (20).

The recent introduction of trastuzumab (Herceptin) may be of interest for
the elderly population, as this form of treatment appears fairly well tolerated.

Another anticancer agent - capcitabine (Xeloda) has been compared with CMF in women older than 55 years (median age 69 years). This study suggests that capcitabine is very effective (RR 25% versus 6%) and well tolerated (except hand and foot syndrome and diarrhea). Its oral formula facilitates administration (21).

The taxanes, both paclitaxel and docetaxel are also used in all groups without particular difficulties in the elderly.

REFERENCES


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Chemotherapy of lung cancer in the elderly

KEYWORDS: Lung Neoplasms + drug therapy; Aged

Lung cancer remains the leading cause of cancer-related death in Europe and North America. It causes 28% of all cancer death, more than breast, prostate, colorectal and ovarian cancers combined, upon the American statistics (1). More than one half of patients with lung cancer are older than 60 years, and 30% are 70 years or older at diagnosis. Approximately 80% of all these patients belong to the non-small cell histologic subtypes. Large majority of these elderly patients, just like younger ones are diagnosed as advanced stage of disease, where curative therapeutic approach is not possible. These patients are candidates for palliative chemotherapy and/or radiotherapy.

The role of chemotherapy in the treatment of advanced non-small cell lung cancer (NSCLC) has been better defined in the meta-analysis from 1995 (2) and just published ESMO minimal clinical recommendation: cisplatin-based chemotherapy prolongs survival, improve quality of life and symptom control in metastatic NSCLC. Impact of chemotherapy (survival advantage of six weeks over best supportive care) in the different subgroups of patients is not clearly defined by the results of meta-analysis and other relevant papers. Are patients in advanced NSCLC and older than 65 years good candidates for chemotherapy?

Older patients have an increased prevalence of diseases and thus they often have multiple and, frequently, interacting diseases. Functional impairment and decreased performance status in elderly patients are the consequences of comorbidity rather than the cancer itself (3). The decreases in functional reserve and the increased comorbidity may make patient really old - in such situation, when general health status interfere with the management of cancer, patient older than 65 or 70 years are not candidates for chemotherapy. Having physiological rather than chronological age as an important criteria, two broad groups of patients 65 to 85 years old may be considered. The first group includes elderly patients requiring specialized care not dissimilar to that provided to younger patients and the second group includes the frail patients who are at high risk to develop life-threatening toxicity and require individualized treatment. As a result of above-mentioned considerations, in the clinical practice, elderly patients either do not receive chemotherapy or receive less aggressive treatments compared to younger ones.

For doctors who treat older NSCLC patients one of the great concerns is risk of early death (less than 30 days from the start of chemotherapy). In the

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