drugs, incomplete repair of DNA damage, impaired apoptosis and increased expression of MDR-1 gene. Older patients also appear to be at special risk for severe and prolonged myelosuppression and mucositis, as well as cardiomyopathy and neuropathy. Of special interest is also chemotherapy and anemia-related fatigue in elderly.

To minimize these complications, certain measures must be taken, namely dose adjustment of drug to GFR, correction of anemia, use of antidots (G-CSF, dexrazoxane, amifostine, pyridoxine), prophylactic use antibiotics in neutropenia, fluid resuscitation in diarrhea and mucositis.

A number of new drugs allow the safe treatment in elderly because of favorable toxicity profile. These include gemcitabine, vinorelbine, and taxanes in low-weekly doses (8). A variety of older chemotherapeutic drugs remain useful. Anthracyclines should be administered by continued IV infusion on small daily doses. Mitoxantrone or liposomal form of drug may substitute doxorubicin.

Palliative therapy must be integrated into treatment plan of elderly patients, and one can always use some form of it.

So, we may conclude with the following:
1. Old age carries important risk for development of cancer (but not obligatory).
2. Advanced age alone is not reason enough for withholding effective treatment that could improve survival and/or quality of life.
3. Treatment of elderly with cancer must be individualized according to CGA.
4. To define best form of treatment, old people must participate in clinical trials.
5. Geriatric oncology will be an interesting area for future research.

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Do clinical trials help us to optimize chemotherapy in the elderly? The lymphoma experience

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

Malignant non-Hodgkin's lymphomas in the elderly are a rather common condition in medical oncology; nevertheless these conditions probably require a specific therapeutic approach. The issue is relatively controversial. Specificities of this subpopulation have been brought to attention of hematologists and medical oncologists only a decade and a half ago, when European School of Oncology Organized the first and second intercity meeting on management of non-Hodgkin's lymphoma in the elderly.

SPECIFICITIES OF PRESENTATION OF NON-HODGKIN'S LYMPHOMA IN THE ELDERLY POPULATION

The first fact that emerged by a revision of several series of non-Hodgkin's lymphoma (NHL) patients in the late eighties of the last century provided the information that at least 34%-37% of all lymphoma patients is aged over 65.

The most frequently observed histological pattern was that of a diffuse large cell lymphoma belonging to the intermediate or high-grade group according to the working formulation. In some series the diffuse large cell pattern accounted for up to 84% of all lymphomas in the elderly. Some observations claimed that the frequency of intermediate and high-grade histology among elderly patients did not significantly differ from the one observed in younger patients. However large case series confirmed that low-grade histology and follicular growth patterns are less frequently represented in the elderly group.

Another characteristic of the non-Hodgkin's lymphoma in the elderly was that initial extranodal presentation or extranodal diffusion found in 45-50% patients ate the onset. The extranodal presentation or involvement might provide an additional risk or bad prognostic factor.

Another risk factor might be provided by the fact that decrease of total T cells accompanied or not by inverted helper-suppressor ratio is more marked in the elderly than in the total population of non-Hodgkin's lymphoma patients. Altered organ sensitivity to drugs, especially the age-dependent decrease in

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the number of stem cells in the bone marrow, seems to be the crucial factor, according to broad clinical experience, in determining the degree of tolerance of patients to cytostatic agents in general.

GOOD NEWS

Several studies have tended to demonstrate that elderly patients are able to tolerate standard dose doxorubicin based regimens and even more aggressive regimes such as full dose ProMACE-CytaBOM in a similar way as younger patients.

The conclusions of a retrospective analysis of SWOG clinical studies, dealing with diffuse large cell lymphoma, suggests that patients over 65 years and younger adult patients with相同 clinical characteristics obtain a similar complete response rate when treated with a comparable dose of chemotherapy, and that there is no correlation between age and toxic side effects from CHOP.

According to German Study Groups including the Kiel Lymphoma Study Group, in unfavorable lymphomas of elderly people as well as in those of the younger population, incidence of toxicity, grades of toxicity and results of treatment were equivalent to those observed in younger patients.

According to results from several prospective clinical studies of efficacy of different lymphoma related chemotherapy regimens ranging from the standard dose CHOP to the aggressive ProMACE-CytaBOM there appeared to be absolutely no difference in tolerance to chemotherapy and treatment results between the elderly and non-elderly population of high-grade lymphoma patients.

BAD NEWS

In most studies of different chemotherapy regimens designed for high-grade non-Hodgkin’s lymphomas the inclusion criteria were unfit for the elderly group. They included limited age distribution (mostly up to 65, exceptionally to 70 years, usually the population aged between 65 and 70 years being poorly represented), normal bone marrow, liver and renal function, normal cardiac function, performance status 0 or 1 and no significant comorbidity.

In a study reported by Miller and Jones patients over 65 years had a relatively mild toxicity with CHOP at initial doses reduced to 50% of the calculated full dosage. However 70% of patients received only 2 to 4 courses because of prolonged myelosuppression and were shifted to other treatment modalities. Thus this experience points to the fact that patients who are likely to need more prolonged treatment (patients with aggressive lymphoma stage III or IV) might not be able to receive CHOP even at reduced doses without significant toxicity. An Italian study comparing full dose CHOP to a specifically designed regimen for the elderly reported 30% toxic deaths on full dose CHOP in a population of elderly patients who otherwise would not completely fill criteria to be included in a classical chemotherapy trial because either of performance status or comorbidity.

The EORTC lymphoma group in a retrospective study of elderly patients suggested that evaluation of toxic deaths in the elderly could be more difficult than in younger patients because the effects from tumor progression, comorbid states deterioration and side effects of chemotherapy are often similar and hardly distinguishable.

Therefore, regimens specifically designed for elderly patients have been developed and analyzed in single arm or randomized trials. The results remain highly controversial. There is still no consensus whether chemotherapy regimens for elderly patients with non-Hodgkin’s lymphoma should be full dose doxorubicin containing or whether development of non-anthracycline containing regimens is warranted. On the other hand a number of these studies suffer from the pitfall in asking for a performance status 0 or 1 and absence of comorbidity, conditions which are not very common in the elderly and even less common in elderly patients with lymphoma.

The problem is further complicated by the poor compliance to treatment in up to 60% of the aged patients.

Age has been identified in some studies as the most important prognostic factor in aggressive NHL.

MAJOR PITFALLS IN THE INTERPRETATION OF CLINICAL TRIALS FOR ELDERLY LYMPHOMA PATIENTS

In a study reported 3 years ago we tried to analyze the impact of several potential prognostic factors affecting the results of elderly lymphoma patients treatment in clinical trials.

We recruited 47 elderly patients (over 65 years,) with aggressive non-Hodgkin’s lymphomas, chemotherapy naive, who were treated with two non-anthracycline containing combinations (BCNU-etoposide-procarbazine and mitoxantrone-etoposide-procarbazine). Both regimens achieved a response rate of 60% with a more modest percentage of complete responses; in several patients with partial response, complete response was achieved with additional involved field radiotherapy. The survival in both arms was identical.

Since the response rate and survival were identical in both arms, we fused all patients together in order to analyze the impact of prognostic variables.

The clinical stage (II, III or IV) had no impact on survival.

The sex (male or female) had no impact on survival.

Presence or absence of bulky disease had no impact on survival.

Performance status (patients being divided in two groups, PS 0+1 and PS 2+3) had a survival impact; the difference in survival was on the significance level of p=0.045 (Figure 1).

![Log rank test, \( \chi^2 = 4.02, \ p = 0.045 \)](image)

**Figure 1. Impact of performance status on survival of elderly patients with diffuse large cell lymphoma**

The impact of comorbidity was enormous. Difference of survival of patients with significant antecedent or concomitant disease and those who were negative for significant comorbidity was statistically significant on the level of p=0.0004 (Figure 2).

![Log rank test, \( \chi^2 = 12.37, \ p = 0.0004 \)](image)

**Figure 2. Effect of comorbidity on survival of elderly patients with diffuse large cell lymphoma (SACD + = significant antecedent or actual comorbid states are present; SACD neg = no significant antecedent or actual comorbid states)**
Breast cancer in elderly 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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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, plateaus 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 227 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-