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.

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Chemotherapy of lung cancer in the elderly

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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 to 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 criterion, 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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Italian retrospective analysis carried out on a database of 1128 patients treated with cisplatin-containing regimens, the incidence of early death was found to be associated with age. It ranged from 0.5% in the patients with less than 55 years to 12.5% in older than 70 years, suggesting a possible relationship with chemotherapy toxicity, especially bone marrow suppression (4). On the other hand, prospective studies often include only very well performing patients (PS 0.1) without significant comorbidities. Results of such designed studies are usually encouraged, but at the expense of selection bias.

The recent development of several active antineoplastic agents for the treatment of NSCLC has created new possibilities for the management of this disease, free of cisplatin. Very few specific studies have been conducted to test the role of chemotherapy in elderly NSCLC patients. First, and most cited is ELVIS (The Elderly Lung cancer Vinorelbine Italian Study Group) study from 1999 (5), where patients were randomized to receive vinorelbine or best supportive care only, with primary end-point quality of life and survival as secondary end-point. It was planned 350 patients, but investigators stopped the recruitment after 160 patients because of the low enrollment rate. There was a statistically significant survival advantage for patients receiving vinorelbine (MST 28 vs. 21 week, 1-year survival 22% vs. 14%), and quality of life (QoL) scores (functional and cancer-related) were better, but not reaching statistical significance. Toxicity-related symptoms were reported to be worse in the vinorelbine group. To evaluate whether the addition of gemcitabine to vinorelbine improves survival and QoL, in the same population Southern Italy Cooperative Oncology Group randomized patients older than 70 years to receive vinorelbine (V) or vinorelbine plus gemcitabine (V+G). On 120 evaluable patients difference in median survival was almost 3 months (29 vs. 18 weeks), and V+G therapy was also associated with a clear delay in symptoms and QoL deterioration (6). It was not easy for the authors to explain such survival gain. They found that the higher number of patients who did not progress in the first three months (50% vs. 30%) could be one of the explanations. They also stressed that the occurrence of toxic death in three patients with multiple unfavorable conditions at diagnosis suggests an exclusion of patients with high scores of comorbidity (Charson score) irrespective of their performance status.

The role of taxanes in elderly population with advanced NSCLC is also under investigation in last few years: Hainsworth et al. reported (7) a phase II study with weekly docetaxel (35 mg/m2) on 39 patients older than 65 years. RR was 18%; median survival was 5 months and 1-year survival 27%. Fidias et al. presented (8) results of phase II study with weekly paclitaxel on 35 patients: RR was 23% and median survival 10.3 months. It seems that weekly administration of newer agents could increase dose intensity with acceptable toxicity, and it offers attractive options for the development of combination regimens.

In the retrospective analysis of prospectively conducted trials for advanced NSCLC from 1990 to 2000, at the Institute for oncology and radiology of Serbia 364 patients were treated with cisplatin-based chemotherapy (120mg/m2). Out of this number 54 patients were older than 65 years. It is interesting to notice that 31 of them were treated from 1990 to 1995 in trials including 271 patients (11.5%) and 23 out of 93 patients in the trial performed 1998-2000 (24 %). Patients' characteristics are shown in Table 1: median age was 68 years and the large majority of patients had good performance status (0.1). Overall response rate was relevant (21%) but less than in whole investigated population (30-34%). Toxicity (Table 2) was moderate, not different from that observed in whole study population. These preliminary results suggest that patients over 65 years, with good PS and preserved renal function should not be excluded from clinical studies where high doses of cisplatin are investigated.

Since the end of 1970s chemotherapy has become therapy of first choice in small-cell lung cancer (SCLC) but again a considerable number of older patients have been untreated. It was thought at the end of 80s that oral etoposide, as one of the most active agents against SCLC could be an attractive candidate for use in older patients. At that time several groups reported encouraged results: Smit et al. (9) administered oral etoposide for 5 consecutive days at dose of 160 mg/m2 to 35 patients, majority of them had extensive disease, and PS 2 or 3. Response rate was 71%, median survival 16 months in limited and 9 months in extensive disease. Clark et al. (10) used a more protracted schedule, giving oral etoposide for 14 days (50 mg twice daily) and the treatment was repeated every 21 day. Response rate was 85% with modest toxicity and excellent survival results. Carney (11) treated elderly patients with good PS and RR of 79% was achieved.

The enthusiasm for use of oral etoposide has been tempered after the results of two randomized British studies in the middle of 1999. MRC Lung Cancer Working Party (12) found on 339 patients in randomized study that combined chemotherapy (CAY or etoposide-vindesine) is superior over oral etoposide in terms of median survival (183 vs. 139 days) and toxicity. London Lung Cancer Group reported (13) similar results on 155 patients randomized to receive alternating CAY/PE or oral etoposide: RR (61 vs. 39%) and median survival (189 vs. 146 days) favored combined chemotherapy arm. WHO toxicity grade III and IV were uncommon in both arms. Evans et al. (14) made a relatively successful compromise combining oral etoposide with carboplatin 150 mg/m2 every three weeks: RR was 71%, median survival 59 weeks for limited disease and 46 weeks for extensive disease. They recorded 10 episodes of febrile neutropenia and 4 sepses, all during the first course of chemotherapy, and grade 3-4 anemia in 75% of patients.

Considering particularly appropriate regimen for the initial treatment of elderly patients with SCLC, cisplatin-etoposide (PE) may be chosen, because it is less myelosuppressive than cyclophosphamide or doxorubicin-based regimen. Also, in the predictive models developed by Radford and Stephens (15,16), two drug regimens were associated with less severe toxicity and fewer septic deaths. Furthermore, the available data suggest that older patients tolerate cisplatin well although renal function decreases with advanced age. In circumstances in which preexisting renal dysfunction or neuropathy exists or aggressive hydration is problematic, carboplatin could be substituted for cisplatin without apparent loss of therapeutic efficacy.

In conclusion, all older advanced lung cancer patients with good performance status and without significant comorbidities and who desire treatment should be offered chemotherapy. No evidence so far exists to support the view that untreated patients live longer or have better quality of life.
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