The role of adjuvant chemotherapy in treatment of non-small cell lung cancer

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Summary: Lung cancer is the most common oncological malignancie. Incidence is growing constantly despite of all efforts of prevention. Amount male population lung cancer is the leading cause of oncological mortality. This article represents review of the most important randomized trials regarding adjuvant chemotherapy of non-small cell lung cancer.

Key words: lung cancer, adjuvant chemotherapy, platinum-containing regimen.

Morbidity of lung cancer (LC) has a first place among malignant tumors in male. More then 75 % of LC cases are non-small cell lung cancer (NSCLC) [1]. It also takes leading place among reasons of cancer mortality in the world. 1.2 millions of new cases and about 1 million of deaths are registered annually [2, 3]. Moreover 5-year overall survival (OS) in majority of countries don't oversize 20-30 % [4]. It takes first place in the structure of cancer mortality among male in Ukraine, morbidity is 37.8 per 100 thousands of population, and mortality – 29.69 per 100 thousands of population [5]. Epidemiological and statistic data indicate that LC is very serious medical and social problem [4, 6].

For a long time therapy of NSCLC stage I-IIIA was limited only surgical treatment. Even in case of radical operations 5-year OS was unsatisfactory: 67 % in patients with stage IA (T1N0M0) and 23 % in patients with stage IIIA(T1-3N2M0) [7]. The main reason of death was distant metastases. This fact indicates systemic character of the disease even at the moment of diagnosis. The analysis of radical surgical treatment, which was performed in different clinics around the world, showed that 5-year OS was no more then 29.9 % [4, 8]. Despite of constant improvement of surgical treatment there wasn't detected serious tendency to the improvement of survival for last three decades [9].

Thereby unsatisfactory results of surgical treatment connected with local relapses and distant metastases show the necessity of adjuvant therapy of operable patients [9]. Adjuvant chemotherapy (ACT) is part of standard cancer treatment after the operation in patients with breast cancer and colorectal cancer long time, but only in last decade it was recommended for patients with early stages of NSCLC. Investigators had contrary

opinions on the results of ACT at the end of XX century. The first metaanalysis of 52 randomized trials compared efficacy of ACT with supporting treatment or observation performed in 1995 showed significant increase of 5-year OS on 4 %. By the results of metaanalysis platinum-based regimens significantly increase survival, and using of alkylate agents showed purer results in comparison with observation [10].

The analysis of two studies, ECOG and ALPI-EORTC, didn't show the improvement of treatments results with ACT usage in patients with stage I-II-IIIA in comparison with observation group. Patients with stage II-III of NSCLC after radical operation were included into ECOG study [11]. 4 cycles of ACT with EP regimen (cisplatin 60 mg/m^2, day 1 and etoposide 120 mg/m^2 day 1-3) followed by radiotherapy total dose 40.5 Gy were conducted in the basic group. Patients from control group received only radiotherapy in postoperative period. Median survival in basic group was 38 months, in control group – 39 months (p=0.56). 3-year survival was 50 and 52 months, respectively. Observation period was 44 months. In ALPI-EORTC study [*12*] were also included patients after radical operation with stage I-IIIA of NSCLC. Patients from basic group received 3 cycles of ACT with mitomicyn, vindesine and cisplatin. Patients from control group were under observation after surgical treatment. The analysis of study results didn't show the difference in overall and relapsed-free survival in both groups.

The similar study BLT, conducted in Great Britain, compared the efficacy of cisplatin-based ACT and observation in patients with stage I-II-III. One of regimens was used in patients: vinorelbin+cisplatin, mitomicyn+ifosfamid+cisplatin, vindesine+cisplatin ,or mitomicyn+vinblastine+cisplatin. There weren't detected the difference in overall and relapsed-free survival in the groups [*13*].

Results of large-scale trial IALT

(International Adjuvant Lung Cancer Collaborative Group Trial) dedicated to the studying of ACT efficacy in NSCLC patients were published in 2004 [14]. Patients with stage I-III after radical surgery were enrolled to the study and randomized in two groups to receive 3 or 4 cycles of ACT cisplatin+vinblastine or vinorelbin+etoposide. Comparison was performed with the group of observation. In some centers adjuvant radiotherapy was prescribed. 148 patients from 33 countries were enrolled. After 56 months of observation significant increase of 5-year OS was registered in the group of ACT by 4.1% (44.5% vs. 40.4%, p< 0.03) and 5-year relapse-free survival by 5.1%

(39.4% vs. 34.3%, p< 0.003). The results showed advantage of ACT in patients with stage II-III of NSCLC [15]. The toxicity analysis revealed the presence of neutropenia grade III-IV in 88 % of patients and febrile neutropenia – in 7% of patients.

The efficacy of ACT with vinorelbine in patients with stage IB-III of NSCLC after radical operation (basic group) was analyzed in the ANITA study [*16*]. Control group was composed of patients under observation. The results confirmed high toxicity rate of the regimen vinorelbine + cisplatin (neutropenia grade III-IV in 86% of patients and febrile neutropenia – in 9% of patients). The distant results showed increase of survival in patients who underwent ACT. Median OS was 65.8 months in basic group vs. 43.7 months in control group (P = 0.0131). 5-year OS was 51% vs. 43 % , respectively (p = 0.013). The study showed significant advantage of ACT in patients with stage II and IIIA of NSCLC after radical surgery and didn't show same results for patients with stage IB. Median survival was 76 months [10, 15].

Patients with stage IB and II (excluding T3N0) of NSCLC were enrolled into the JBR10 study [17]. After the surgical treatment patients were randomized into group of ACT (vinorelbin + cisplatin) and group of observation. Significant increase of 5-year OS on 15% was observed in the group of ACT (p = 0.012) [15].

Patients with adenocarcinoma of lung with stage I (T1-T2N0M0) after radical operation were enrolled into the JLCRG study [18]. They received tegafur 250 mg/m^2 during two years. Patients from control group were under observation. Significant increase of 5-year OS on 11% was observed in patients with T2N0M0 from the group of ACT with minimal toxicity rates [15].

Results of 5 large-scaled studies (ALPI, BLT, IALT, JBR10,ANITA) were combined in the common database LACE (Lung Adjuvant Cisplat in Evaluation). The analysis of treatment results of 4584 patients revealed increase of survival in the group of ACT from 64% to 67% for stage IB, from 39% to 49% for stage II, and from 26% to 39% for

stage IIIof NSCLC. The results also showed the decrease of survival in the group of ACT in the group of patients with stage IA. Observationperiodwas 5.1 years [*19*].

Renewedin 2007 results of metaanalysis of NSCLC collaborative group (1995) included data of 30 randomized trials and 8147 patients. They showed significant increase of 5-year OS in the group of cisplatin-based ACT on 4 % (from 60% to 64%) [*20*].

Results of tree another randomized trials with similar design and regimens of ACT showed increase of survival in the group of patients with stage II-III of NSCLC after radical operations. In all these studies combination of cisplatin dose> 80 mg/m^2 was used. Regimen cisplatin + vinorelbine was used more often [*10*].

Thereby, ACT improves relapsed-free and OS in patients with stage IB-IIIof NSCLC. For today the most appropriate and effective is cisplatin-based ACT. ACT with two-compound cisplatin-based regimens should be started after the restoration of patient's performance status after surgical treatment (1-2 months) [21].

Despite of achieved success results of the treatment in this group of patients are unsatisfied, therefore the search of new drugs and regimens of ACT in patients with NSCLC is being continued.

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