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Treatment options in stage III non-small cell lung cancer – short review

Opțiuni terapeutice în cancerul pulmonar non-small cell stadiul III – scurtă recenzie

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Abstract

Lung cancer is responsible for over 1 million deaths annually, worldwide. The disease becomes symptomatic in advanced stages, so the diagnosis is delayed and 90% of cases cannot benefit from a curative treatment. In NSCLC surgical resection represents the best option for long term survival in resectable stage III and in clinical stage I/II. Patients with stage IIIB or IV usually receive chemotherapy or palliative treatment. For patients with no driver mutation detected platinum based combination chemotherapy is the first choice. Definitive radiotherapy is considered an alternative for patients who are not candidates for combined modality treatment. When a stage IV cancer is diagnosed based on an isolated metastasis, the patient's benefit from the removal of the metastasis and of the primary tumor if it is resectable. The prognosis in NSLC is mainly influenced by the TNM stage at diagnosis. The rate of survival decreases in opposing correlation with the stage of the cancer. Poor performance status, reduced lung capacity, weight loss, vascular invasion are indicators for a poor prognosis.

Keywords: ***stage III, lung cancer, treatment***

Rezumat

Cancerul pulmonar este responsabil pentru mai mult de 1 milion de decese anual la nivel mondial. Boala devine simptomatică în stadiile avansate, astfel încât 90% din cazuri sunt diagnosticate tardiv și nu pot beneficia de un tratament curativ. În NSCLC rezecția chirurgicală reprezintă cea mai bună șansă de supraviețuire pe termen lung, atât în stadiile III rezecabile, cât și în stadiile I/II. În stadiile IIIB și IV de obicei se inițiază terapie sistemică sau paleativă. În cazul pacienților fără mutație detectată, prima linie de chimioterapie o constituie asocierea a doi agenți chimioterapici, dintre care un derivat de platină. Radioterapia reprezintă o alternativă în cazul pacienților care nu pot beneficia de chimioterapie sau chirurgie. Pacienții cu metastază unică și tumoră primară rezecabilă pot să beneficize de metastazectomie și rezecția tumorii primare. Prognosticul în NSCLC este influențat în principal de stadiul TNM la momentul diagnosticului. Stadiul avansat al bolii, statusul clinic al bolnavilor, alterarea funcției respiratorii, scăderea ponderală, precum și invazie vasculară, reprezintă indicatori ai unui prognostic rezervat.

Cuvinte-cheie: ***cancer pulmonar stadiul III, tratament***

Lung cancer in today's perspective

Lung cancer has become the leading cause of cancer related death all over the world, with over 1 million deaths annually[1]. The main risk factor for lung cancer remains tobacco smoking. The association between smoking and lung cancer was first described in 1950[2]. Since then, the prevalence of smoking has increased and today cigarette smoking is responsible for 70% of age specific death rates in men and a less significant increase in women[3]. The incidence of lung cancer in individuals who have never smoked (defined as less than 100 smoked cigarettes in their lifetime) is estimated at 15% in men and 53% in women[4]. These findings suggest the involvement of other risk factors such as genetic features: epidermal growth factor receptor gene pathway (EGFR) alteration, the human repair gene (hMSH2) polymorphism, reduced activity of gluthatione-S-trasnferase enzymes. Other possible risk factors are viral infections, airflow obstruction, air pollution, and occupational carcinogens (arsenic, asbestos, beryllium, cadmium, ethers, nickel, silica)[5]. Regarding race and ethnicity, reports show a lower incidence of lung cancer among Hispanics[4]. Also, black people have a higher mortality rate than white patients. The incidence of lung cancer is higher in men than in women[4].

The histopathological classification of lung tumors includes: epitelial tumors, mesenchymal tumors, lymphohistiocytic tumors, tumors of ectopic origin and metastatic tumors. In the malignant epitelial tumors group are: adenocarcinoma , squamos cell carcinoma, neuroendocrine tumors[4].

Lung cancer becomes symptomatic frequently in advanced stages, so the diagnosis is delayed and 90% of cases can not benefit from a curative treatment[5]. Clinical features include weight loss, dyspnea, cough, stridor, chest pain haemoptysis, superior vena cava syndrome, hematological abnormalities, and signs of paraneoplastic syndromes. Treatment options and prognosis depend on the histopathological type, TNM staging and patients' performance status. The 5 year survival is between 50% for stage IA and 2% for stage IV[6].

The extension of locoregional disease with correct staging must be carefully assessed in patients who may be candidates for surgical treatment. The necessary preoperative investigations are bronchoscopy, functional respiratory tests, thoracic and upper abdominal computed tomography (CT) scan. If surgery is still an option after these investigations, lymph nodes involvement must be examined by mediastinoscopy with biopsy or PET-CT scan before surgical

intervention. In patients with squamous cell type of cancer and lymph nodes smaller than 1.5 cm, these investigations may be omitted[1]. In SCLC staging should include the search for bone and cranial metastasis by scintigraphy, cranial CT scan or magnetic resonance imaging (MRI)[5].

Due to continuous increase of lung cancer incidence and the poor prognosis associated with this disease, an appropriate screening algorithm has been sought. According to the National Comprehensive Cancer Network (NCCN) guidelines published in 2012, all patients between 55-74 years old with a history of 30 pack-years, active smokers or less than 15 years since they gave up smoking, should have a low dose CT scan performed annually. The same should be done for patients with the same age range, but a history of 20 pack-years and at least one additional risk factor (history of cancer, history of COPD or pulmonary fibrosis, family history of lung cancer, or occupational exposure)[7].

TNM staging

The staging of lung cancer depends on the tumor's characteristics (T), lymph node involvement (N), presence of the metastasis (M). The revised TNM staging from 2009 (7th Edition) the characteristics of stage III lung cancer include the presence of N1 involvement if it is associated with T3 more than 7 cm or T3 with multiple nodules in the same lobe. The noncontiguous pleural involvement has been upgraded as part of stage IV. The presence of T3N0 has been moved to stage IIB[8,9]. So, stage III includes IIIA (T1/T2 with N2, T3 with N1/N2, T4 with N0/N1) and IIIB (T4 with N2/N3, any T with N3). Stage III A is divided in two categories: less advanced or "non-bulky" and "bulky" (the short axis of the lymph node more than 2 cm, groups of small lymph nodes, evidence of extracapsular involvement, more than 2 lymph stations affected)[10]. This classification is used to establish the surgical opportunity. A correct TNM staging is based on a proper assessment of the lung and mediastinum. The involvement of the lymph nodes is an important factor to assess the resectability of a NSCLC. The lymph nodes' invasion evaluation is initially based on imagistic criteria (HRCT or PET). In cases with potentially resectable disease (T2-T4) with N1 involvement, invasive mediastinal staging is indicated, even if the mediastinum appears clean on HRCT/ PET[11].

Treatment options for NSCLC

Surgical resection represents the best treatment for long term survival. Candidates are chosen accordingly to preoperative stage (I, II, IIIA), lung performance status (FEV predicted post operatory>1L), smoking status, presence of comorbidities, patients approval[9,12]. Patients with stage IIIB or IV usually receive systemic therapy or palliative approach. When a stage IV cancer is diagnosed based on an isolated metastasis, the patients benefit from its removal and chemotherapy of the primary tumor[9,13].

Surgery in stage III

Surgical resection remains an important option in specific stage III and in clinical stage I/II which were found to have pathological stage III. In almost 20% of cases the lymph node involvement can not be proven using EBUS or mediastinoscopy[14]. In patients with clinical stage I/II in whom invasion of the lymph nodes is not proven preoperatively, surgery and adjuvant chemotherapy are the treatments of choice.

Patients with T3N1 have better prognosis than patients with T3N2, even though both categories are considered IIIA[8,9]. The initial option for these patients consists of surgical resection followed by adjuvant chemotherapy in cases with completely resected disease. In patients with potentially resectable Pancoast tumor (T3-4N1M0) chemoradiotherapy followed by surgery is the preferred approach. Patients with nodules within the same lobe as the primary tumor or those with tumor nodule(s) in a different ipsilateral lobe, without mediastinal nodes, may also be candidates for surgery.

In patients with stage IV cancer due to solitary nodules in each lung and negative mediastinoscopy, under the presumption of synchronous unrelated cancer, surgery and chimiotherapy are to be considered[15]. Surgery is rarely used in T4N0-1 disease, but there have been reports of survival rates up to 50%[16]. Patients with N2-3 involvement, with invasion of mediastinum, major blood vessels, vertebral column, trachea, esophagus and heart (stage III B NSCLC), are treated with chemoradiotherapy.

Adjuvant therapy

The benefits of adjuvant chemotherapy were first analyzed in 1970. Given the lack of evidence on improved survival and the poor tolerance, adjuvant therapy was not widely recommended. In 1995 for the first time a meta-analysis stipulated that patients might benefit from adjuvant cisplatin-based chemotherapy[17] . Today, based on several large studies, adjuvant platin based chemotherapy with or without adjuvant radiotherapy is used in patients with stage IB, II and IIIA[17,18,19]. There are no randomized trials in which different platinum based adjuvant chemotherapies are compared. Still the guidelines recommend the use of a platinum salts regimen associated with a third generation cytotoxic agent such as gemcitabine, docetaxel, vinorelbine[17,18]. On the other hand, targeted agents have no indication as adjuvant treatment outside a clinical trial setting, even in the presence of an activating mutation[17]. Adjuvant chemotherapy initiation remains to be discussed on each case according to the size of the primary tumor, node invasion, histopathological type, and activity on PET-CT. In stages IB evidence of benefits are less conclusive. However, there are several trials (LACE metanalysis) in which adjuvant therapy improved overall survival in stage IB[19] . Adjuvant chemotherapy is preferred to neoadjuvant treatment due to the possibility of a more accurate staging. There are no significant differences between them in terms of survival[17,18]. Induction chemotherapy may be a possibility in patients with low-volume medastinal disease or microscopic N2 involvement.

For patients in advanced stages in whom surgery is not an option, concurrent chemoradiotherapy (CCRT) is the treatment of choice. If CCRT is not possible induction chemotherapy followed by definitive radiotherapy is the alternative.

Systemic therapy

The purpose of chemotherapy (CT) or targeted agents is to prolong survival in patients with advanced NSCLC. The choice of the systemic agent depends on the initial evaluation of the patient with NSCLC. This evaluation includes: assessment of a driver mutation (EGFR, ALK, ROS1, BRAF, HER2, DDR2, MEK1- some of them in use only in clinical studies), programmed death-ligand 1(PD-L1) pathway, clinical status, the presence of metastatic tumor, previous treatment, and patient consent. For patients with no driver mutation detected, cytotoxic chemotherapy is to be considered as initial therapy (6 cycles of platinum based agent associated with bevacizumab, followed by maintenance therapy (bevacizumab, erlotinib) until progressive disease occurs[17]. In case of progression nivolumab or other non-cross-resistant agent which was not included in the original regimen are initiated. For cases of tumors with driver mutation, specific inhibitors (erlotinib, afatinib, crizotinib) are to be considered initial treatment, until the first evidence of progression. In this case recommendations include second line of targeted therapy or nivolumab immunotherapy followed by an agent which was not included in the original regimen[20].

For patients with squamous histopathological subtype, no molecular tests for driver mutation are necessary. Platinum based combination chemotherapy, possibly associated with gemcitabine is consider first choice. If the disease progresses, nivolumab immunotherapy is the option, followed by docetaxel and ramucirumab or other non-cross-resistant agent which was not included in the original regimen[21] **.** Single agent therapy includes widely used drugs (pemetrexed, docetaxel) or agents in phase II clinical trial (gemtacibine, paclitaxel, vinorelbine, topotecan, irinotecan). Docetaxel is preferred in squamous cell carcinoma; it may be used in non-squamous histopathological type in patients with progression after therapy with pemetrexed; it has a higher toxicity than pemetrexed [21]. In cases with progression after combination therapy, alternative combination regimens did not improve overall survival compared with single agent treatment[22]. Neither did the combination therapy with single agent chemotherapy and a targeted agent[23].Targeted agents are used in tumors which contain a driver mutation as the initial line or in case of relapse after initial chemotherapy. Systemic therapy is usually administrated at a three or four weeks interval, no more than 6 cycles. However, in patients in whom neurotoxicity is a concern, a lower dose regimen can be chosen, weekly[24]. Retreatment with the same regimen may be applied in patients who were stable for at least 6 months after treatment discontinuation or in patients who received maintenance with bevacizumab after the initial response[25]. In case of progression, a non-cross resistant therapy is preferred. In resectable NSCLC there are no strict rules regarding strategy in case of relapse after surgery and adjuvant chemotherapy. However, the preferred algorithm is to consider progression if the relapse occurs in less than six months and to consider first line chemotherapy if the relapse appears after one year[17]. The period between 6-12 months is to be analyzed individually by each physician. In case of progressive disease during the initial treatment or the maintenance phase, treatment targeted against specific sites of metastases may be a benefit.

Radiotherapy

The benefits of adjuvant radiotherapy (RT) are seen in cases where mediastinal lymph node involvement is suspected after CT scan, but not confirmed, in cases with N2 and those with positive resection margins. RT for all cases with stage III is not confirmed in randomized trials. However, in subgroup analysis, patients with N2 lymph node involvement have an improved five-year survival rate after adjuvant radiotherapy[26,27]. In contrast, in the presence of N1 with adjuvant chemotherapy, RT had a negative effect on survival, but a favorable effect in patients without adjuvant CT[28]. Regarding obtaining positive surgical margins, the adjuvant RT is administered sequentially after adjuvant CT. There is no evidence that radiotherapy may improve prognosis in patients with carcinoma in situ. The main adverse effect of thoracic radiotherapy, cardiotoxicity, has decline after 1989 due to technical improvements[29]. In 1970, a phase III trial of the Radiation Therapy Oncology Group established the regimen of radiation of 60Gy in 30 daily fractions, once daily radiation plan. This option is still considered optimal today[30]. Definitive RT is considered an alternative for patients who are not candidates for combined modality treatment[31]. In patients with dysphagia, hemoptysis, tumoral airway obstruction or those with a poor performance status, old or with relapse, palliative RT can be used[32]. Even though patients with stage III NSCLC are at high risk of brain metastasis, there isn't proofs that prophylactic cranial irradiation increases survival[33].

Prognosis

The prognosis in NSCLC is mainly influenced by the TNM stage at diagnosis. Survival decreases progressively with increasing staging. Poor performance status, reduced lung capacity, weight loss, vascular invasion also induce a poor prognosis. Regarding histopathological classification, it has been shown that poorly differentiated tumors have worse prognosis, but there is no clear statement to make a distinction between histopatological subtypes[17] .

Discussions

In lung cancer, irrespective of the treatment applied, there is always the risk of locoregional relapse or distance metastasis. This fact has raised a question: which therapeutic approach is better? Several uncontrolled phase II studies suggested a survival benefit of neoadjuvant chemoradiotherapy followed by surgery[34]. This was not confirmed by two large randomized phase III trials[35,36]. The first included 429 patients with N2 involvement proven by biopsy and whose tumors were considered resectable. These patients were divided into either concurrent chemoradiotherapy followed by surgery and another chemotherapy, either by concurrent chemotherapy[35]. The second trial involved 579 patients with N2 biopsy-proven, who were treated with surgery versus radiotherapy after induction chemotherapy[36]. Regarding IIIA, the subgrup analysis concluded: patients should achieve a complete resection, lobectomy after induction therapy is preferred to chemo-radiotherapy alone, pneumonectomy has a higher risk of death and should only be performed in quality surgical facilities[35,36].

In front of an unresectable disease (N2-3 involvement, with invasion of mediastinum, major blood vessels, vertebral column, trachea, esophagus, heart) chemotherapy with concurrent radiotherapy is the standard approach. First, it was believed that sequential administration improves 1 year survival, due to avoiding overlapping toxicities[37]. However, multicenter randomized phase III trials have proved the superiority of concurrent chemoradiotherapy compared with sequential treatment in longer follow-up[38,39]. Large tumors, with indication of RT and with high risk of radiation pneumonitis due to increase radiation volume, may benefit from induction chemotherapy prior to concurrent chemo-radiotherapy. Regarding consolidation therapy (additional cycles of chemotherapy after concurrent chemo-radiotherapy), there are no results in its favor[40,41]. All these results have been summarized in the NCCN and ESMO guidelines so that the patient could benefit from a proper therapeutic strategy. Regardless of the chosen treatment, whenever possible it should be initiated immediately, rather than delayed.

In conclusion, lung cancer remains one of the most aggressive types of cancer with a high mortality rate in spite of combined treatment. That is why there is a continuous research for methods that should improve prognosis. ■

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