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Review

Medical anticancer treatment of lung cancer associated with comorbidities: A review

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ABSTRACT

Comorbidities are frequent in patients with lung cancer, who are often treated with systemic anticancer therapy. The purpose of the present review is to report the adaptations recommended for the various drugs used in lung cancer treatment, in the context of a specific comorbidity. The literature was reviewed for neurologic, endocrine, hepatic, renal, digestive, cardiovascular, pulmonary, blood and systemic diseases. The comorbidities impact on the systemic anticancer treatment is poorly assessed. There are no good data with a high level of evidence and literature is often limited to experts' opinion and to case reports. We need to improve our knowledge about those patients by adequate multicentric and prospective studies and registries in order to offer them better care in term of evidence-based medicine.

1. Introduction

Comorbidities are frequent in patients with lung cancer, the most lethal cancer, accounting for 25% of the deaths by cancer (Eurostat 2014). The Eindhoven cancer registry in the Netherlands collected 3864 lung cancer between 1993 and 1995 [1]. Only 34% did not have a concomitant disease. The most frequent were cardiovascular disease (23%), followed by chronic obstructive lung disease (COPD) (22%), other malignancies (15%), hypertension (12%) and diabetes mellitus (7%). The prevalence of co-morbidity was higher for patients > 70 years (69%) than for younger patients (52%) and was 8% higher for men than for women. More recently, the role of comorbidity for non-surgically treated lung cancer was studied in the Danish lung cancer registry [2]. Of the 20,548 patients, 50% had a least one comorbidity. The most frequent was COPD found in 10% of the patients followed by other malignancies (9.1%), diabetes (6.1%), cerebrovascular disease (4.6%), and peripheral vascular disease (3.6%). In a series of 4447 elderly Medicare beneficiaries with lung cancer [3], 39% had COPD and 13% had congestive heart failure (CHF). In a series of 484 cases of small cell lung cancer (SCLC) diagnosed at the Innsbruck University Hospital and associated institutions between 1991 and 2011 [4], cardiovascular disease was present in 56.9%, COPD in 51.9%, other malignancies in 19.7%, diabetes in 19.7%, neurologic disease including stroke in 11.9% and renal failure in 7.4%.

A systematic review on the impact of comorbidity on chemotherapy use [5] performed on 34 studies published between 1990 and 2009, including 12 with lung cancer, reported in majority a decreased use without significant effect on survival. In a population of 58,498 cancer patients newly diagnosed between 1995 and 2002 in the registration area of the Eindhoven Cancer Registry [6], on 6690 non-small-cell lung cancers (NSCLC) and 1629 SCLC, 581 and 157 were, respectively, associated with diabetes. The administration of treatment with diabetes was not significantly reduced but survival was worse.

Comorbidities are thus frequent in lung cancer patients and most of them are treated by various therapeutic approaches including by chemotherapy. It should be noted that those patients are excluded from the clinical trials and we have thus no good data about the adaptation of systemic anticancer treatment to the underlying comorbid condition. The purpose of the present review is to report in the context of lung cancer the adaptations that are recommended for the various drugs used in the context of a specific comorbidity.

2. Methods of the review

As sources of data, we used PubMed, pharmaceutical industry notices, and personal bibliography. We focused our review on

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the following drugs: adriamycin (doxorubicin), afatinib, amrubicin, bevacizumab, carboplatin, CCNU, cetuximab, cisplatin, crizotinib, cyclophosphamide, docetaxel, erlotinib, etoposide, gefitinib, gemcitabine, ifosfamide, irinotecan, methotrexate, mitomycin, paclitaxel, pemetrexed, raltitrexed, teniposide, topotecan, vinblastine, vincristine, vindesine and vinorelbine.

Only cases or series of patients with lung cancer and a preexisting or simultaneous comorbidity were considered. Synchronous cancers or secondary comorbidity occurring after starting anticancer treatment were not taken into consideration for the present review. When available, specific data regarding lung cancer patients are presented. Otherwise, we extrapolated data from case reports/series reported in other cancers or from extensive reviews for the drugs commonly used in lung cancer patients.

Each group of comorbidities was reviewed by a particular physician and all authors have agreed on the whole manuscript content.

3. Cardiovascular diseases

The following MESH terms were used to identify the relevant bibliography: heart defect, congenital vascular malformation, cardiovascular abnormalities, heart disease, arrhythmias, atrial fibrillation, cardiomyopathies, heart failure, heart failure-diastolic, heart failure-systolic, heart valve diseases, myocardial ischemia, coronary diseases, vascular diseases, cerebrovascular disorders, stroke, and hypertension.

A preexisting history of congestive heart failure or arrhythmia prior to the diagnosis of lung cancer treated by radiochemotherapy has to be associated to the occurrence of future cardiac complications [7]. New ischemic changes or arrhythmias were documented but none were fatal. In multivariate analysis performed after combining the lung cancer series with oesophageal cancer patients, a preexisting cardiac history marginally predicted the risk of later complications. The authors did not describe the cytotoxic drugs that the patients received.

A retrospective analysis of a randomised trial [8] in advanced NSCLC comparing two chemotherapy regimens (cisplatin-gemcitabine versus epirubicine-gemcitabine) failed to show a significant association between an history of cardiac disease (myocardial infarct, aortic stenosis, mitral valve regurgitation) and left ventricular ejection fraction (LVEF) decline after chemotherapy. It should be noted that a LVEF < 45% measured by multiple gated (MUGA) scan was a criterion of exclusion to the trial.

However, as some drugs like anthracyclins, could lead to decreased LVEF, they have to be used with caution in patient with pre-existing LVEF. Administration of large hydratation volume, as for cisplatin or ifosfamide, should also be considered in patients with pre-existing reduced LVEF at risk of pulmonary oedema (experts' opinion).

Antiangiogenic drugs should be used very cautiously in patients with vascular malformations. A case report of a patient with a cerebral arterio-veinous malformation and non-small-cell lung carcinoma treated by bevacuzimab was associated with death from massive cerebral haemorrhage due to a vascular rupture [9].

4. Pulmonary diseases

The following MESH terms were used for respiratory comorbidities: pulmonary disease, chronic obstructive; asthma; bronchoconstriction; pulmonary fibrosis; lung disease, interstitial; pulmonary emphysema; alpha-1 antitrypsin deficiency, autosomal recessive; respiratory distress syndrome, adult; respiratory tract infections.

The available data, mainly from Japan, deal with interstitial lung disease. Even if the prevalence of pulmonary fibrosis in general population is similar in Japanese and Caucasian populations [10,11], generalisation of observations to occidental countries has to be done with caution. Retrospective studies have assessed the efficacy of chemotherapy in patients with pre-existing interstitial lung disease (ILD) and advanced lung cancer [12–14]. Responses rates appeared similar to those observed in patients without ILD but prognosis was worse. Potential explanations for that observation are exacerbation of ILD during chemotherapy and lower rates of administration of second-line treatments. Data are limited concerning specific anticancer regimens. However, some authors have concerns about toxicity of chemotherapy in those patients, mainly regarding acute exacerbations of ILD under chemotherapy. In a retrospective analysis [15] including 83 patients, both NSCLC and SCLC combined, this complication occurred in 6 among 83 patients during 1st line chemotherapy and in 4 among 28 patients during second-line. The regimens were mainly carboplatin-paclitaxel for NSCLC and cisplatin-etoposide for SCLC.

In case of SCLC, chemotherapy is recommended in any case because of the severe prognosis due to the neoplastic disease [14,16]. Some authors [17] point the risk for ILD exacerbation with platinum and etoposide regimen, particularly when given as second- or third-line chemotherapy but this risk is counterbalanced by survival improvement. Suzuki et al. [18] have proposed topotecan for salvage chemotherapy in case of pre-existing ILD because of the low incidence of exacerbation with that drug. Nevertheless, a case of diffuse alveolar damage has been published in that situation [19]. Amrubicine, a new anthracyclin, used in the management of SCLC in East Asia, has been shown to be associated with a very significant increased risk of severe ILD in case of pre-existing fibrosis and is thus considered as contra-indicated in such a condition.

For chemotherapy of NSCLC, the number of publications on the topic is limited. Three regimens seem relatively safe: cisplatin and vinorelbine with an ILD exacerbation of 16% [13]; platinum derivative and etoposide or carboplatin and paclitaxel, both without exacerbation [16]. The number of cases published is however small and thus cautious is required.

Tyrosine kinase inhibitors (TKI) have a well documented pulmonary toxicity with the development of ILD. Asian populations appear particularly at risk. ILD due to gefitinib is ten times more frequent in those populations than in Caucasian ones. Risk factors for developing ILD under TKI therapy [20,21] are male gender, tobacco-smoking history, poor performance status and pre-existing pulmonary fibrosis. Case reports suggest that in case of ILD occurring during gefitinib therapy, good improvement with steroids and lack of poor prognosis features like early onset of ILD, retreatment by erlotinib might be proposed without major risk of ILD aggravation [22].

The administration of TKI in patients with preexisting pulmonary fibrosis has been the topic of studies for erlotinib and gefitinib. The presence of an ILD on a standard chest X-ray is a very significant risk factor for developing a TKI-induced ILD but it is not the case if lesions are only seen on the CT scan [23]. That observation leads the authors to recommend avoiding TKI in patients with radiological signs of lung fibrosis on standard X-ray and being careful if they are apparent only on CT scan. That guideline is nevertheless controversial because of case reports publications where the administration of gefitinib in patients with preexisting ILD has not been detrimental [24].

A special situation is the reintroduction of a TKI after regression of a TKI-induced ILD. This has been successfully performed in association with corticotherapy administered according to various dosages [22,25]. The literature does not allow recommending a specific schedule.