Editorial

Adjuvant chemotherapy for locally advanced non-small cell lung cancer: still state of the art or an outdated therapy?

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For early-stage non-small cell lung cancer (NSCLC), anatomical pulmonary resection remains the gold standard for the treatment (1). About one-third of NSCLC patients are diagnosed with locally advanced diseases (2). From UICC stage IIB and above, multimodal treatment is recommended, consisting of either surgical resection followed or preceded by chemotherapy, depending on tumor size or lymph-node involvement combined with radiation therapy (1). Adjuvant chemotherapy (AC), cisplatin combined with vinorelbine, was introduced in the therapy of NSCLC to decrease the risk of local recurrences. Since three randomized controlled trials (RCTs) on AC demonstrated a significant survival benefit, AC was included in the guidelines (3-5). However, due to a variety of reasons, the actual implementation of the guideline, particularly the administration of AC, is partly questionable.

Désage *et al.* performed a multi-center retrospective analysis of 588 patients who underwent curative-intent lung surgery between 2009 and 2014. In fact, 210 patients had a theoretical indication of AC (6). The study's primary endpoint was to determine compliance with AC guidelines in real-life practice and to observe if AC was delayed for any reason (6). Furthermore, the authors examined which patient population deviated the most from guideline-based AC. In this study, 131 patients (62.4%) received guideline-based AC. The main reasons for non-compliance to AC guidelines were age (27.8%), major comorbidities (24.1%), and altered recovery and postoperative complications (24.1%). The authors' multinomial regression analysis demonstrated that those three parameters were independent factors for non-compliance to AC guidelines.

Since current guidelines suggest, most patients in their cohort received either cisplatin combined with vinorelbine (86.3%). According to guidelines, AC should be initiated within 4-8 weeks following lung surgery (1). Désage *et al.* demonstrated that postoperative complications, length of stay in the hospital exceeding 14 days, and an early referral to a rehabilitation unit were independent factors for the delay of the administration of AC (6).

AC is known to have partially severe side effects, ranging from nausea, and vomiting to neutropenia and renal failure (7). Désage *et al.* showed a discontinuation rate of approximately 20% in their analysis due to the toxicity of AC. Furthermore, only 45.7% of the whole group completed all AC cycles. In the other cases, patients needed dose reduction.

Désage *et al.* present real-life data concerning the daily decision-making progress in multi-disciplinary tumor board meetings (MDT). Non-compliance to AC guidelines due to age and comorbidities is a daily practice. Blasi *et al.* included 140 patients aged 75 years or older who underwent surgical resection for lung cancer with a formal indication of AC. Of these patients, only 21% received AC (8). However, low rates of guideline- based AC have also been described

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in younger patients (<70 years). Rodriguez *et al.* included ninety-nine patients with a theoretical indication of AC in their analysis. Only 55% of the cohort received AC in according to the guidelines (9). Age is supposedly the most frequent factor for the denial of AC. In the study of Rodriguez *et al.* only 25% of older patients >70 years in the cohort received guideline-based AC (9).

The reason for omitting guideline-based AC is usually due to the assumption that there is a mismatch between the benefit for survival and the toxicity of the administered AC (10).

For instance, patients with prolonged postoperative courses are often not treated with guideline-based AC. Therapy is started late >8 weeks or shortened due to the significantly prolonged recovery. These are usually individual decisions in which the patient's wishes should also be considered. For patients undergoing curative-intent lung surgery with severe comorbidities, AC is frequently omitted. Comorbidities were an independent factor for non-compliance to the guidelines of AC in the study of Désage *et al.* (6). This patient population is underrepresented in studies. In RCTs, patients with specific comorbidities, like coronary heart disease, are often excluded from the outset (11,12). In the study of Désage *et al.*, 24.1% of patients did not receive guideline compliance AC due to comorbidities. Leiter *et al.* conducted a simulation study identifying specific comorbidities associated with a higher morbidity or mortality rate if AC is administered in guideline compliance. They found that older individuals with cardiac comorbidities may be better managed with observation than AC (13).

Age was the most crucial factor for non-guideline-based AC in the study of Désage *et al.* (6). Interestingly, discontinuation or dose reduction did not differ significantly between patients older- and younger than 70 years. Blasi *et al.* stated that AC in stage II–III NSCLC in selected patients aged 75 years or older was able with a manageable toxicity profile and good long-term results (8).

Désage *et al.* demonstrated that patients receiving guideline-based AC showed significantly better survival than patients with non-guideline AC (6). Of course, these survival data should be treated with caution, as the authors compare patients who are too old or sick for guideline-based AC with patients who receive guideline-based AC and are healthier. However, the authors aim to show with this analysis that guideline-based AC continues to provide a significant survival benefit (3,5,8).

After two decades of little development beyond cisplatin-based chemotherapy, adjuvant immunotherapy approaches are ready to have a transformative impact on the treatment paradigm of NSCLC. Hopefully, epidermal growth factor receptor (EGFR) antagonists will be included in AC. The phase II EVAN trial showed significantly improved two-year survival of patients with an EGFR mutation treated with Erlotinib with a better tolerability profile than guideline-based AC (14). The CTONG1104 phase III trial comparing Gefitinib with guideline-based AC showed a significant benefit for the disease-free interval (15). Upcoming neoadjuvant/adjuvant immunotherapy trials will help to improve adjuvant therapy both in terms of overall survival and the toxicity of the therapy (16).

In summary, the study of Désage *et al.* reported that although AC use in real-life practice might differ from the guidelines, AC administration has a survival benefit and is well-tolerated in most patients. The authors highlighted that decision on AC administration is influenced by the patient's clinical conditions, which is why the discussions should always be justified and decided by the MDT on an individual patient.

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