Pulmonary Alterations During BEP? Always Be Aware Of BIP

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Even in the era of targeted therapies, systemic treatment of patients with metastatic germ-cell cancer of the testis using conventional chemotherapy remains one of the major successes in medical oncology. According to the International Germ-Cell Cancer Collaborative Group (IGCCCG) classification, this group of mostly young patients can be divided into three different prognostic groups. Applying the current standard chemotherapeutic regimen consisting of bleomycin, etoposide, and cisplatin (BEP), durable complete responses can be achieved in more than 90, 75, and 50% of the patients belonging to the good, intermediate, and poor risk group, respectively [1].

This impressive anti-tumor activity of BEP is however at the expense of severe toxicities, both in the short and long term. The most important long-term toxicity is the occurrence of cardiovascular events. Compared to the general population, it is estimated that patients previously treated with BEP have a 2- to 7-fold increased risk to experience a cardiovascular event, which thereby clearly affects the ultimate outcome of these patients [2]. One of the most feared short-term toxicities is the occurrence of bleomycin-induced pneumonitis (BIP). The exact incidence of BIP remains unclear as diverse studies use different criteria for establishing the diagnosis. As a result, reported incidences range from 0 to almost 50% of the patients receiving bleomycin-containing chemotherapy. It is estimated that approximately 3% of all patients receiving bleomycin die from BIP [3]. In other words, BIP accounts for approximately 30% of the deaths occurring in the group of patients with good risk metastatic testicular cancer.

The most important strategy to take in patients developing BIP is the cessation of further bleomycin administrations. Therefore, it is of utmost importance to diagnose BIP as early as possible. The establishment of BIP however is rather cumbersome as symptoms and signs of patients developing BIP are non-specific and resemble several other disease conditions

that frequently occur in cancer patients including pneumonia, lymphangitis carcinomatosa, and heart failure. Most predominant clinical symptoms and signs encompass a non-productive cough and exertional dyspnoea, gradually increasing in severity, while at physical examination bibasilar crepitations can be found. The most specific features at radiological examinations are interstitial infiltrates, but a whole spectrum of other radiological alterations has been reported to occur in the context of BIP, further hindering its diagnosis [3]. A decrease in the transfer capacity of the lungs for carbonic monoxide (TLCO) has long been considered a pulmonary function assessment specific for the detection of BIP and to be predictive for its development. However, the finding that treatment with etoposide and cisplatin (EP) alone also induced deteriorations in TLCO [4] convincingly showed that this parameter does not adequately reflect bleomycin-induced pulmonary damage in case bleomycin is given combined with EP. Consequently, the TLCO can not serve as a marker for early diagnosis of BIP.

In this issue of ONKOLOGIE, von Rohr et al. [5] describe a patient experiencing BIP, who showed an increased uptake of ^{18}F -fluorodeoxyglucose (FDG) in the lungs at FDG-PET scanning. After complete resolution of BIP, both clinically and radiologically, pulmonary uptake of FDG normalized as well. Given the chronological course in this case and the fact that an inflammatory process is thought to underlie BIP [3], it is indeed likely that bleomycin-induced pulmonary damage was reflected in alterations at PET scanning. However, as the authors discuss in their article, other lung diseases including sarcoidosis, infections, and lymphangitis carcinomatosa [6] can give rise to similar abnormalities at PET scanning. All these conditions, including sarcoidosis, which has been suggested to be associated with seminoma [7], can occur during treatment for metastatic germ-cell cancer. So, pulmonary changes observed at FDG-PET scanning in patients undergoing bleomycin-containing chemotherapy are non-specific for BIP.

Nevertheless, whether or not such changes can be used as an early marker for BIP deserves further study in a properly designed prospective trial.

Even more important than diagnosing BIP at an early stage may be the identification of patients who are at high risk to develop BIP since there are valid chemotherapeutic alternatives for BEP. 3 cycles of BEP is the standard treatment for patients with good-risk disease, but it is generally felt that 4 cycles of EP yield equivalent outcomes [8]. For patients with intermediate or poor risk testicular cancer 4 cycles BEP is standard. 4 cycles with etoposide, ifosfamide, and cisplatin (VIP) are an alternative in view of similar anti-tumor activity in a randomized study [9].

In order to classify patients at high risk of developing BIP, several factors have previously been revealed. Age is an important one, since the risk to develop fatal BIP increases with every decade above 30 years. Disturbed renal function also contributes to a higher chance for BIP. Bleomycin is mainly cleared by the kidneys as a consequence of which impaired renal function prolongs bleomycin clearance and augments

bleomycin-induced lung effects. Other established risk factors include the total bleomycin dose, a smoking history, and widespread metastatic disease [3]. In recent years, it has been attempted to further improve the identification of patients at risk to develop BIP by the use of pharmacogenomics. For example, bleomycin is inactivated by the enzyme bleomycin-hydrolase. Several polymorphisms in the encoding gene exist, which result in different enzymatic activity of bleomycin hydrolase. The genotype in this gene was however not associated with the occurrence BIP [10], but research exploring functional polymorphisms of other genes involved in the metabolism of bleomycin or in the pathogenesis of BIP is ongoing.

Through such approaches and through better insight into the underlying mechanisms, it is likely that the identification of patients at risk to develop severe chemotherapy-related untoward events will further improve. This will hold true not only for BIP but also for other toxicities including cardiovascular events. Undoubtedly, this increase in knowledge will contribute to an even better prognosis for patients presenting with metastatic germ-cell cancer.

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