

Importance of pneumonitis induced by taxane-based chemotherapy and chemoradiotherapy for esophageal cancer

Esophageal cancer is the eighth most common cancer worldwide. The main therapeutic option for patient with locally advanced or metastatic esophageal and gastroesophageal junction cancer is chemotherapy. In localized cases or in order to improve swallowing additional radiotherapy may also be used.

Palliative chemotherapy alone is not known to provide any survival advantage, but it may improve quality of life in patients with metastatic or inoperable esophageal cancer. Response rate of the most commonly used chemotherapeutic regimens (containing platinum derivative) is 30-57%, if the chemotherapy contains taxane this rate is 35-55%. Complete remission is quite rare (0-11%).^[1-3] Using a two-drug combination is recommended first-line, but tree-drug regimen can also be administered in case of medically fit patients with good general condition. Using docetaxel in combination with cisplatin and 5-fluorouracil is one of the standard therapeutic options in the first-line treatment of patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction.^[2] Squamous cell cancer (SCC) seems to be more sensitive to chemotherapy, chemoradiation and radiotherapy than adenocarcinoma, but the long-term outcome appears to be the same.

Radiotherapy is another important treatment modality in case of localized esophageal cancer; earlier it was the conventional therapeutic method, but its efficacy alone is poor. Strategies designed to enhance local control include improved tumor targeting (three dimensional treatment planning and increasingly more sophisticated radiotherapy techniques), escalation of thoracic radiotherapy dose or usage of different fractionations. The practice of advanced techniques should reduce acute and late

treatment-associated toxicity. Intensity modulated radiotherapy (IMRT) is currently being investigated. Retrospective studies comparing three dimensional conformal versus IMRT for patients with esophageal cancer have generally shown superior dose conformity and homogeneity with IMRT and reduction of radiation dose to the lungs and heart.^[4]

Individualized combinations of different therapeutic procedures, such as combining radiotherapy with chemotherapy tend to improve local control and survival.^[5] The most frequently applied third-generation chemotherapeutic agents are taxanes. Paclitaxel is a prototype of taxane family and an excellent radiosensitizer. Definitive chemoradiation with carboplatin and paclitaxel was well-tolerated resulting in superior locoregional control, overall and disease-specific survival.^[5] Pre-operative induction chemotherapy with docetaxel and cisplatin followed by chemoradiation was effective and was associated with improved overall and disease specific survival of patients with SCC or adenocarcinoma of the esophagus. In a phase II randomized trial the response rates of induction paclitaxel-based chemotherapy followed by concurrent chemoradiotherapy combined with paclitaxel and 5-FU or cisplatin were examined. The endpoint of 1-year survival did not meet a predetermined benchmark and the regimens were associated with substantial morbidity and 3-6% mortality. Based on these induction therapy in itself may place patients at risk of complications during their definitive treatment as well as an important side-effect it may cause an increased rate of radiation pneumonitis.^[6]

It is well-known, that radiosensitization has been reported to increase therapeutic efficacy, but it may also increase therapy-induced toxicity. In case of radiotherapy for chest tumors radiation pneumonitis seems to be one of the most important acute toxicities, especially in the setting of combined concurrent chemoradiation. This unfavorable side-effect is often a dose-limiting factor, which influences the therapeutic outcomes and the patients' quality-of-life. Clinically, significant radiation pneumonitis occurs in 10-20% of patients.^[7] Acute radiation injury typically develops 2 weeks to 3 months after treatment and is

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usually limited to the irradiated field. Mild injury often heals on its own without treatment, whereas more serious injury results in fibrosis 6-12 months after therapy.^[8] The pathogenesis is uncertain, but appears to involve both direct lung tissue toxicity and an inflammatory response. Corticosteroids may be effective, if started early in the course of the disease. It is not known unambiguously which dosimetric parameter optimally predicts the risk of radiation pneumonitis. Mean lung dose, V20 and V30 are the most studied parameters.^[7] In another article, dosimetric factors were not associated with the development of symptomatic pneumonitis.^[6] Some studies demonstrated that preexisting pulmonary lung dysfunction, tumor location in lower lobes and use of concurrent chemotherapy could improve the risk of radiation pneumonitis.^[7]

According to the Summary of product characteristics paclitaxel (Taxol®) may play a role in the development of interstitial pneumonitis especially in case of patients receiving concurrent radiotherapy and/or gemcitabine independently of the order of therapeutic options. Respiratory disorders, such as acute respiratory distress syndrome, interstitial pneumonia/pneumonitis, interstitial lung disease, pulmonary fibrosis and respiratory failure (maybe associated with fatal outcome) can be found in the summary of product characteristics of docetaxel (Taxotere®).

SUMMARY

In my opinion, the foregoing pulmonary disease was caused by the combined taxane-based treatment, mainly by the concomitant chemoradiotherapy (without strong correlation with radiation dose). It was possibly aggravated by the first line chemotherapy, which might have sensitized the lung tissue to radiation damage in esophageal cancer patients.

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