CT evaluation of side effects of EGFR-inhibitors used in a group of patients affected by non-small cells lung cancer (NSCLC)

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Aims and objectives

With the development of biological drugs, such as monoclonal antibodies, new scenarios are opened in the treatment of many pathologies both neoplastic both inflammatory.

In the management of neoplastic patients radiologists are not just asked to evaluate the response to the therapy but they also should know the side effects of the drugs taken by the patients in order to report them to the referring physician and to make a correct diagnosis of the radiological findings.

Monoclonal inhibitors of Epithelial Grow Factor Receptor (EGFR), which belongs to the group of Tyrosine Kinase Inhibitors (TKI) drugs, are recently started to be used in in the treatment of Non Small Lung Cell Carcinoma (NSCLC) in advanced stage with promising results.

We decide to evaluate the side effects, detectable at CT scan, of EGFR-inhibitors in a group of patients affected by NSLCC in advanced stage to evaluate if any new side effects of these drugs could be found and to confirm or disconfirm what is known the literature.
Methods and materials

A retrospectical evaluation of the Total-Body Contrast Enhanced CT scans (TB-CECT) of 30 patients was made by three radiologists in order to have a triple blind evaluation.

The inclusion criteria to enroll the patients were the following: patients with a diagnosis of NSCLC in advacend stage, under treatment with anti-EGFR inhibitors, at least three months of therapy with anti-EGFR (crizotinib, erlotinib, gefinitib) and at least two TB-CECT scans to compare: before and after the treatment.

A review of the literature about the EGFR inhibitors' toxicity was made to know what are the known side effects of EGFR-inhibitors, detectable at CT scan. We classified the known side effects, detectable at CT scan, of EGFR-inhibitors as follow dividing them into organs.

**Brain:** haemorrage and posterior leuckoencefalophathy

**Lung:** capillary leak syndrome and parenchimal ground glass opacities (GCO). GCO, according to the literature, was subclassified into four groups: a) a non specific area with ground-glass attenuation, b) multifocal areas of airspace consolidation, c) patchy distribution of GCO attenuation accompanied by interlobular septal thickening, d) extensive bilateral ground glass attenuation or airspace consolidation with traction bronchiectasis.

To avoid false positive findingns, just the lung not affected by the neoplamsm or by metastases and not treated with radiation therapy was evaluated.

**Gastrointestinal system:** Steatosis and intestinal bleeding.

To evaluate new onset after therapy of steatosis were used the following criteria: the differential liver-spleen attenuation value on the unenhanced phase measured 10 HU or the absolute CT attenuation of the liver on the unenhanced examination must be less than or equal to 40 HU. To evaluate worsening of already existing steatois an increase at least of 10% of HU liver-spleen attenuation value compared to the pre-therapy value or a decrease of 10% of the absolute HU liver value compared to the pre-therapy value at the unenhanced examination.

**Pancreas:** signs of acute or chronic pancreatitis.

**Bowel:** enteritis, intestinal pneumatosis and ileitis.

**Bladder and soft tissue:** haemmoraggic cystitis, fluid retention and ascites.

Furthermore because in the literature is described (Petrelli et al.) an higher risk with these drugs of Venous and Arterial tromboembolic events (VTEs and ATEs) but not so many
evidences are available, radiological signs of VTEs or ATEs were also considered and in this evaluation we decided to consider these parameters: 1) radiological signs of venous or arterial thrombosis, 2) arterial bleeding, 3) increase, in number (at least two more calcification with an axial or cranio-caudal diameter greater or equal than 3 mm), and in size (at least 10% axial or cranio-caudal increased diameter) of endoluminal parietal calcifications among the arterial vessels.

All the organs were studied in order to find also findings not yet codified in the literature.

Stricts criteria of inclusion of the radiological findings were established with two oncologists and all organs were studied.
Results

10 patients showed positive CT findings codified in the literature as "known side effects": 3 patients showed lung's toxicity, 5 patients showed hepatic steatosis, 2 patients showed ATEs or VTEs.

In 5 patients coprostasis, not described in the literature as a side effect, was observed.

Lung toxicity

Other risk factors for lung consolidation or infectious respiratory disease were excluded by the oncologists, so all the three cases of lung toxicity were correlated to the therapy. Of the three patients one patient had a GCO type a and GCO type b (figure 1), two patients have GCO type a (figure2 and figure 3)

Hepatic steatosis

Among the five of patients with steatosis three had a new onset of steatosis (figure 4) and two were classified as a worsening of existing steatois. Metabolic disorders or diet factors that could influence steatosis were excluded in these patients, so all the five cases of steatosis were correlated to the therapy.

VTEs or ATEs

One case of thrombus of the auricula was found but the patient had a history of atrial fibrillation and so the finding could not be correlated to therapy according with the oncologists.

One case of thrombosis of the internal jugular vein was noticed, but the patient had an omolater port-a-cath; so according with the oncologists these two findings could not be correlated to the therapy.

None case of VTEs or ATEs related to the therapy was detected.

Coprostasis

Coprostasis was a finding seen in five patients (figure 5 and figure 6) not yet known in the literature.

We defined the criteria for coprostasis as the presence of fecal endoluminal material at least at 2/3 of the colic segments with a colic diameter of 2-3 cm, CT signs for the diagnosis of necrotic stercoral colitis were also considered in order to exclude it.
Fig. 1: CT axial scan of the same patient at different level. The upper two figures in the box show the presence at apical right lobe of a consolidation area after therapy. The lower two figure show the presence of GCO areas.
Fig. 2: CT axial scan. Figure shows the presence of GCO at the right lobe after therapy.

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Fig. 3: CT axial scan. Figure shows the presence of GCO areas after therapy.

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Fig. 4: CT axial scan. The scan shows the onset of hepatic steatosis after treatment in one of the patients.

Fig. 5: Axial CT scan. The scan shows the presence of coprostasis in one patient after treatment.
Fig. 6: Axial CT scan. The pictures show in two different patients, the presence of coprostasis after the medical treatment.

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Conclusion

None case of VTEs-ATEs related to therapy was detected in our group, so an higher risk of VTEs and ATEs was not present in the short time after the beginning of the therapy with these drugs.

Colic coprostasis, not yet described in the literature, was a collateral finding present in the 17% of our patients; it could be an useful information for the physician because, according with the oncologists, the stasis of the fecal material inside the colic segments could influence the metabolization of the drugs taken by the patients.

Lung toxicity (10% of our patients) and liver toxicity (17% of our patients) were confirmed as side effects of these drugs and they could appear in the short time after the beginning of the therapy.

So we can conclude that lung's and liver's toxicity should be investigated in the short time at CT scan; in our group there was not an higher risk in the short time of ATEs or VTEs, coprostasis a collateral findings should be notice during follow-up CT examinations and be discussed with the referring oncologist.
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