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PIVOTAL SCREENING AND PROPOSED TREATMENT ALGORITHM FOR IMMUNE CHECKPOINT INHIBITOR-INDUCED CARDIO/MYOTOXICITIES IN NEOADJUVANT-TREATED RECTAL CANCER PATIENTS: EXPERIENCE FROM THE CHINOREC TRIAL

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Background Myotoxicities (myositis, myocarditis or rhabdomyolysis) are rare (incidence 0.21%) but potentially life-threatening immune-mediated adverse reactions (IMARs) of immune checkpoint inhibitors (ICI), such as ipilimumab (IPI) or nivolumab (NIVO), with a case fatality rate (CFR) of up to 40%. The true incidence is likely to be underestimated and may not be representative for neoadjuvant treatment approaches in gastrointestinal (GI) cancers, especially in combination with chemoradiotherapy (CRT). Currently the summary of product characteristics (SmPC) does not suggest any pre-emptive screening and surveillance for myotoxicities.

Methods The CHINOREC study (NCT04124601) is an ongoing prospective, randomized, open-label, multicenter, phase II investigator-initiated trial (IIT). Patients with locally advanced rectal cancer (LARC) receive either neoadjuvant CRT (50 Gy + capecitabine 1650 mg/m²/d PO) alone or in combination with a single dose of IPI 1 mg/kg IV and 3 cycles of NIVO 3 mg/kg IV Q2W, with subsequent surgical resection in a curative intend. Patients are continuously screened at baseline and throughout the whole study period for cardio/myotoxicity biomarkers, such as creatine kinase (CK), creatine kinase muscle-brain (CK-MB), myoglobin (MB), troponin T (TnT) and N-terminal prohormone brain natriuretic peptide (NT-proBNP).

Results From 06/2020-03/2022, 24 patients were randomized to the CRT+IPI/NIVO arm. Out of these, 4 patients (16%) developed a biopsy-proven myositis, of whom 2 (8%) were symptomatic (1 patient with a grade 4 SAE). All patients were promptly initiated with medical interventions in a step-up approach, starting at the first time of elevated cardio/myotoxicity biomarkers (regardless of symptoms). Patients received prednisolone 1-2 mg/kg with concomitant intravenous immunoglobulin (IVIG) 2 g/kg. If myotoxicity biomarkers did not improve, patients received plasma exchange (PLEX) and if further ineffective, infliximab 5 mg/kg IV. To this date all patients have resolved back to normal CK and MB levels. Although all myositis patients had strikingly elevated TnT (median peak 330 ng/L, 95% CI 39-3097) and NT-proBNP levels (median peak 655 pg/mL, 95% CI 507-1161) myocardial involvement/overlap could not be proven by cardiac magnetic resonance imaging (MRI), transthoracic echocardiogram (TTE), electrocardiography (ECG) and/or coronary computed tomography angiography (CTA). However, myocardial biopsies were not performed due to safety concerns.

Conclusions Patients receiving neoadjuvant ICI with CRT should be closely monitored by myotoxicity biomarkers for potentially severe ICI-induced myositis to initiate early counter treatment in a step-up approach. Highly elevated TnT values were observed despite the lack of myocarditis in cardiac diagnostic work-up. As treatment for ICI-induced myositis will concomitantly treat potential cardiotoxicity, myocardial biopsy may be debatable.

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Trial Registration NCT04124601

Ethics Approval The study protocol was verified by the "Ethics Committee of the Medical University of Vienna" (EC No. 2040/2019).

Consent Written informed consent was obtained from the patient for publication of this abstract. A copy of the written consent is available for review by the Editor of this journal.

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