RESEARCH TOPIC CLI18

A roadmap to increase survival in oral cavity cancers: clinical trials to predict and intercept the malignant transformation of oral potentially malignant disorders and to treat oral cavity cancers

Research area
Medical Area

Clinical Unit name
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Abstract
Background and rationale
An estimated 350,000 new cases of oral squamous cell carcinoma (OSCC) are diagnosed globally each year, with a 5-year overall survival rate of roughly 50%; the diagnosis is frequently made at a late stage. Lesions in the oral cavity that pose a risk of developing into cancer are known as oral potentially malignant disorders (OPMD); they are quite frequent (global prevalence of 4.5%) and they carry a risk for malignant transformation of 15.3% in dysplastic cases (4.8% to 51.3%). Incisional biopsy combined with histological analysis is the conventional procedure for evaluating the mucosa; nevertheless, it is invasive, and it should be repeated frequently to rule out the risk of cancerization. Oral brushing represents the ideal tool to continuously monitor patients, as being easily implementable in different clinical settings, non-invasive and potentially as informative as histological assessments.
Once diagnosed with a risk of cancer transformation, the issue of cancer interception becomes crucial, by intervening on molecular/immunological factors that could lead to cancerization. One of this strategy, called “immuno-interception” aims at eliminating neoplastic lesions at their earliest stages by mobilizing a specific immune response. Preliminary results showed that patients with oral proliferative leucoplakia who were treated with anti-PD1 nivolumab experienced a regression rate of 37%. However, even in presence of regression, malignant transformation may happen, and the systemic immunotherapy is not without toxicities that are less acceptable in patients with pre-malignant conditions.
Cluster of differentiation 40 (CD40) is a co-stimulatory receptor of the tumor necrosis factor (TNF) receptor superfamily. CD40 is expressed on numerous cell types, including antigen presenting cells such as dendritic cells (DCs) and macrophages. Reduced expression of CD40 pathway components has been associated with a higher risk of OPMD malignant transformation6; conversely, activating the CD40 pathway inhibited malignant transformation of OPMD in a carcinogen-induced animal model of oral squamous cell carcinoma. Agonistic monoclonal antibodies to CD40 can: stimulate DCs to activate cytotoxic CD8+ T-cells in the

absence of CD4+ T-cell help; reprogram macrophages to kill tumor cells in a T-cell independent fashion and activate cytotoxic NK cells and neutrophils. Mitazalimab is an agonistic human monoclonal (IgG1) antibody targeting CD40; its intralesional administration may allow a safer and more active stimulation of immune system to modulate the immune equilibrium towards elimination of OPMD.
Instead, when facing a locally advanced OSCC, the prognosis is less favourable, and the risk of locoregional/distant relapse is high even with surgery and postoperative (chemo)radiation approach. Recently, the use of immune checkpoint inhibitor pembrolizumab in neoadjuvant/adjuvant setting has demonstrated a benefit in improving event-free survival (Keynote 689 trial). However, the treatment was offered to all the patients with no selection factors, and the response rate in neoadjuvant setting is limited to about 1 out of 5 patients. In this regard, the combination of chemotherapy and immunotherapy in a selected population of patients with OSCC is a reasonable choice to increase activity in patients more likely to respond and save unnecessary toxicities to patients resistant to the combination of drugs.

The current project for the PhD candidate will be focused on 3 independent clinical trials that have been activated in Humanitas as coordinating center. The candidate will be actively involved in all the phases of these trials, coordinating the participating centers, discussing the clinical activities, closely working with the laboratories and preparing the clinical reports and analyzing the results.

Clinical Trial Nr 1: The “Oris” trial. Evaluating the accuracy of oral brushing in respect to histology for molecular characterization of OPMD.
After the approval of the Ethical Committees, a consecutive series of OPMD patients will be collected. Fifty patients with any type of OPMD will undergo oral brushing. DNA purified from cytobrush will be used to infer the presence of DNA aberrancies by scanning the entire genome for the presence of marked chromosomal imbalances, such as loss of heterozygosity (LOH), gain or loss of genomic material or single nucleotides variants. Conventional cytology will be also performed, and the description of the results will be collected. After oral brushing, a diagnostic biopsy (incisional) or a diagnostic-therapeutic (excisional) exeresis will be accomplished. Clinical characteristics of the enrolled patients will be collected into dedicated electronic case-report forms (eCRF). The following recognized clinical/pathological risk factors for malignant transformation will be collected: sex, age, smoking status, immune suppression, previous head and neck cancer, type of OPMD, site, extension, duration of the lesion and grade of dysplasia. DNA evaluation results (ploidy, LOH) will be compared to assess the accuracy of oral brushing in comparison to histological exam. Sensibility and specificity will be determined. Patients will be followed for at least 3 years and any new oral cavity squamous cell carcinoma that will develop from the OPMD will be recorded.

Clinical trial nr 2: The “Aphrodite” trial. Intralesional mitazalimab (CD40 agonist) to reduce the risk of cancerization of OPMD.
This is a multicentric, prospective, single arm, open label, proof of concept, phase 2 clinical trial. Patients with high-risk clinical OPMD will receive 4 cycles of intralesional mitazalimab 200 mcg per Kg (every 2 weeks +/- 2 days)9. After 6 months since treatment start, patients

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will undergo resection or biopsy. A safety run in cohort assessment is foreseen after the first 6 patients have completed the full treatment. The primary objective is to evaluate the impact of study treatment in terms of best overall response (complete response + partial response rate) at 6 months, as defined by the percent change in clinical pathologic composite score. Secondary objectives are safety, risk of malignant transformation and change in histological grade, and quality of life. The study will be conducted in 6 Italian investigational sites.

Clinical Trial nr 3: the “Persephone” trial. Chemo-immunotherapy in selected CPS-positive oral cavity cancer patients.
The trial is a phase II, single arm, open label, multicenter study that aims to evaluate safety and activity of study treatment combination carboplatin + paclitaxel + tislelizumab as neoadjuvant treatment in locally advanced OSCC patients to reduce the risk of recurrence after primary treatment. Main inclusion criteria are: - Patients with stage III-IV(M0) OSCC according to the VIII edition of AJCC staging system; - Biomolecular criteria: CPS PDL-1 > 1 tumours and CD8+/FOXP3+ ratio > 4 (this parameter has been associated both to OSCC at higher risk of relapse and to tumors with higher responsiveness to immunotherapy). The analysis will be carried out by a central laboratory; - Performance status ECOG 0-1; - Availability of tumour tissue for study purposes.
Patients will be treated for 2 neoadjuvant cycles, then a clinical evaluation will be performed, complemented also by a radiological assessment if deemed necessary. In case of response, then another cycle will be administered followed by surgery; otherwise, patients will go directly to surgery. Postoperative treatment will be given according to Institutional policies. Main endpoint of the trial is the rate of pCR and MPR (i.e. less than 10% viable tumour cells identified on routine haematoxylin and eosin staining in pathological surgical specimen); secondary endpoints are safety and 3-year disease-free survival and overall survival. A minimum follow up of 3 years will be considered.

Scientific references

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Type of contract

Scholarship or coordinated and continuous collaboration contract (Co.Co.Co.) amounting to at least € 35,000 gross per year, activated by Istituto Clinico Humanitas. The amount is subject to IRPEF taxation and to autonomous and full payment of social security and welfare contributions by the collaborator, directly to the relevant professional pension fund or to any other fund of their choice.

Borsa di studio o Contratto collaborazione coordinata e continuativa (cococo) pari ad almeno € 35.000 annui lordi attivato da Istituto Clinico Humanitas. Importo soggetto a tassazione IRPEF e versamento per contribuzione previdenziale ed assistenziale autonomo ed integrale a carico del collaboratore, direttamente alla cassa professionale di competenza o a qualsiasi altro Fondo dallo stesso prescelto.

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