Tailoring different intensity of oncological treatment in elderly head and neck cancer pts

Background

Approximately 30% to 40% of head and neck cancer (HNC) population are elderly patients (pts); in most HNC trials and meta-analysis, they seem not to benefit from intensified regimens, showing worse survival in comparison with younger pts. As there are no data showing that age confers in itself resistance to treatment in HNC, it is plausible that it is the impact of comorbidity and frailty that reflects on survival.
In elderly HNC patients, the benefit of toxic treatments on patient survival could be overwhelmed by the adverse events caused and the risk of competing events (death resulting from comorbid illnesses or treatment related toxicities) should be clearly assessed in the treatment decision making. In this regard, selection of the best treatment option according to patient vulnerability, balancing the risk of acute/long-term toxicities and treatment efficacy is vital; it is also necessary in the context of an intensive treatment to address the need of allocating supportive and rehabilitative resources. The costs of care in HNC is increased by the age, comorbidities, intensity of treatment itself and its associated complications.

Because age alone could not be considered as discriminator for suboptimal treatment choices, geriatric scientific societies recommended:
- To perform elderly-specific clinical trials, with formal geriatric assessment, including the evaluation of comorbidities
- To evaluate predictive models for treatment choice

We lack prospective trials assessing screening tools for multidimensional health problems and geriatric assessment of elderly HNC pts, able to guide the appropriate selection of pts, type and time of therapeutic intervention.
Comprehensive Geriatric Assessment (CGA) is a tool to perform an accurate evaluation of elderly pts; it has been shown to improve functional status, survival and reduce hospitalizations and nursing home stays. In oncology there is strong evidence that CGA may detect unsuspected conditions/unaddressed problems and improves function, outcomes and possibly their survival. The value of other tools (i.e the G8 questionnaire) has been advocated as preliminary screening methods to discriminate pts who should receive the longer and time-consuming CGA.

Hypothesis

By using codified appropriate selection tools we will be able to divide the global elderly population in 3 categories: fit, vulnerable and frail. By modulating treatment intensity accordingly, we can improve expected treatment results and balance the toxicities.

Aims

1) To prospectively evaluate patient with squamous cell HNC ≥ 65 years suitable for a curative treatment in order to assess the utility of incorporating a screening tool based on the frailty index and tailor the treatment intensity accordingly.

The role of the multidisciplinary team, trained and assisted by a geriatrician, will be crucial in selecting the treatment considering tolerance, complications, quality of life and expected survival.

2) To evaluate the supportive and rehabilitative needs in each cohort of pts as defined by the CGA.

Methods

AIMS 1

Patients with a first diagnosis of locally advanced squamous cell of oral cavity, oropharyngeal, laryngeal and hypopharyngeal squamous cell cancer having ≥65 years will be referred to the multidisciplinary team composed by a surgeon, a medical oncologist and a radiation oncologist. By patient clinical evaluation and in presence of prospective study inclusion criteria, the patient will be offered to sign the informed consent to participate to the first part of the study.
The therapeutic approach will be proposed on the basis of the geriatric assessment results: at first, the patients will receive the G8 questionnaire as screening tool, which is a validated instrument for performing screening for frailties. The score ranges from 17 (not at all impaired) to 0 (heavily impaired).
In case of score greater than 14, i.e. **fit patients**, then the choice of treatment will be based on the guidelines of the National Comprehensive Cancer Network (NCCN). We recognize that these are guidelines typically very inclusive and transferable to the every-day clinical activity of a multidisciplinary team, used to assess and treat HNC patients. In particular, we confirm that Italian national guidelines (by Italian Association of Head and Neck Oncology, AIOCC, Medical Oncology Association, AIOM and Radiation Oncology Association, AIRO) are superimposable to NCCN guidelines.

In case of a G8 score of 14 or lower, the patient will receive an added evaluation with a CGA and will be defined as fit, vulnerable or frail.

The CGA consists in a global and comprehensive evaluation, using standardized tools, of several domains of aging such as the functional and motion status (ADL, IADL, Tinetti test),

nutritional status (MNA-SF), cognitive and psychological condition (MMSE and GDS), comorbidities (CIRS-G). It usually also considers polypharmacy, social issues and living environment such as presence or absence of reliable social support and care-giver, presence of architectural barriers or difficulties on access to transportation that can interfere with the care program.

A senior geriatrician, familiar with geriatric oncology, will train investigators on CGA at each Center: in particular, the geriatrician will train clinical oncologist/surgeon to administer a test for cognition evaluation (MMSE Mini Mental State Evaluation) and to collect anamnestic data for comorbidity scale (CIRS-G Cumulative Illness Rating Scale-Geriatrics). Moreover, a separate form on social data and caregiver support, as well as medication intake will be collected.
Oncology nurses will be trained to collect geriatric information on functional status ((activities of daily living (ADL); instrumental activities of daily living (IADL)), balance and motion test, and nutritional status with two different forms (Tinetti score and Mini Nutritional Assessment Short Form MNA-SF).
The data will be reviewed by a senior geriatrician to subdivide the patients into the two categories of frail and vulnerable.

According to the class determined by the CGA, the patients could be defined as “fit”, “vulnerable” or “frail”.

Fit patients will receive standard treatment (see above).

Patients with a **vulnerable** profile according to CGA will receive a de-intensified treatment, according to each tumor subsite. The main principle is to reduce the overall toxicity of the treatment, in order to maintain the adherence to the proposed therapy and to select the right balance between tolerable adverse effect and treatment efficacy.
Hereafter we briefly summarize the rational and the way with which “de-intensification” will be pursued for the main single treatment modalities.

From a radiotherapeutic point of view, since about 95% of locoregional recurrence occur in high risk volume, i.e. macroscopic disease, a de-intensified RT approach will be studied, treating with curative doses only the high risk regions, limiting elective radiation of nodal basins thought to be at lower risk of recurrence.
Besides this approach, for patients with HPV-positive cancer, bi-fractionated RT in spite of conventional fractionation will be proposed in definitive setting or postoperative high-risk patients.

From a surgical point of view, in vulnerable patients no difference in type and extension of surgical resection will be proposed, but reconstructive strategy will take into account patient’s characteristics and specific contraindications. Sophisticated reconstructive surgery is demanding for time under anesthesia requested in the operating room. The choice among different and less demanding reconstruction modalities will be done in a multidisciplinary way and criteria of choice will be registered.

For what concerns chemotherapy, concomitant weekly carboplatin will be administered, instead of cisplatin, and this will be reserved only to HPV-negative oropharyngeal cancer. This reflects the worse prognosis of this group of patients, through the adoption of a well-tolerated radiosensitizing scheme.

Frail patients will receive palliative hypofractionated radiotherapy with/without a split course (cyclic radiotherapy). The purpose of this RT approach is to achieve symptom control and/or significant tumor regression within a short overall treatment time minimizing potential side effects and patients' distress by reducing number of journeys to the RT department. Besides, cyclic hypofractionated RT should permit to administer repeated cycles only in patients showing good tumor response with acceptable toxicity and to limit futile treatment and defer the remaining treatments especially in patients with declined performance status despite palliation of symptoms.

According to a 3-months survey conducted in INT on 50 patients, it is expected that the 3 subgroups will include, respectively, 30%, 50% and 20% of whole study population.
The multidisciplinary team will tailor the intervention plan of supportive care for each patient according to the needs derived from the CGA.

Consensus on the treatment of locally advanced HNC, according to subsite and to the evaluation of the G8 questionnaire and the CGA.
The multidisciplinary group participating to the project obtained a consensus on the treatment of locally advanced HNC, according to subsite and to the evaluation of the G8 questionnaire and the CGA. The results are presented below and will serve as basis for the treatment decision in the trial.

GERIATRIC ASSESSMENT	TREATMENT			
	ORAL CAVITY	**HPV POS OROPHARYNX**	**HPV NEG OROPHARYNX**	**HYPOPHARYNX/ LARYNX**
FIT **G8 total score>14**	According to guidelines	According to guidelines	According to guidelines	According to guidelines
VULNERABLE **G8 total score≤14 and CGA definition of vulnerable**	Surgery + IMRT (no chemo, no elective volume or reduced elective volume) IMRT at curative dose + weekly carboplatin (in case surgery not feasible)	IMRT (no chemo, bifractionated RT on the high risk volume, no elective volume or reduced elective volume). If surgery, de-escalation dose on the high risk volume	IMRT + weekly carboplatin (no elective volume or reduced elective volume)	Surgery + IMRT (no chemo, no elective volume or reduced elective volume) IMRT at curative dose + weekly carboplatin (in case surgery not feasible)
FRAIL **G8 total score≤14 and CGA definition of frail**	IMRT Palliative Hypofractionated RT	IMRT Palliative Hypofractionated RT	IMRT Palliative Hypofractionated RT	IMRT Palliative Hypofractionated RT

AIMS 2

The multidisciplinary team will tailor the intervention plan of supportive care for each patient according to the needs identified in the CGA. Supportive and rehabilitative needs in each cohort of CGA will be registered, with the purpose to analyze the burden of health care requirements in this setting of pts and the differences according to each cohort.
This assessment will be made throughout all the treatment phase and will constitute the basis for any other future interventional trial aimed at reducing the adverse events and to reduce the costs of treatment toxicity from the perspective of the health systems.

Study end-points

AIM 1

Primary end-point

- Fit pts: to replicate the 3-year loco-regional control (LRC) achieved in general population of HNC.
- Vulnerable pts: to reach 3-year LRC not lower than the 10% of that achieved in general population of HNC.
- Frail pts: to maintain the recommended treatment intensity (not lower than 85%).

For primary endpoint we will consider only HPV negative disease; the group of HPV positive oropharyngeal cancer pts will be considered only for descriptive analysis (toxicity, feasibility of the treatment and outcome). There are insufficient data regarding outcome of HPV-positive cancers in the elderly, so that no statistical inference could be made in the present trial. The collected data on elderly HPV-positive pts will serve as assumptions for future trials.

Secondary endpoints:

- Safety of the whole treatment (CTCAE v. 4.0)
- Treatment intensity
- Major surgical complications up to 1 month after surgery: major bleeding, flap failure, fistula formation, infection requiring surgical drainage, and hardware exposure,
- Hospitalization time during the curative phase and within 1 month from treatment end
- Quality of life trajectory (through MDASI-HN: T0 = before therapy; T1 = treatment end)
- Change in CGA classes after treatment

AIM 2

Supportive and rehabilitative needs in each cohort of CGA will be registered, in terms of:

- nutrition: time spent on enteral nutrition
- dysphagia: need of radiological exams, access to swallowing expert visit
- psychological support: need of access to specific services

Moreover, pts will be monitored for unplanned access to hospital (emergency room, outpatient visits).
In order to measure the changes in health status in the pts after treatment, the EQ-5 questionnaire will be administered at T0 and T1.

Statistical methods

For FIT pts, we considered as estimates for general HNC pts population outcome those reported in the Pignon meta-analysis of combined treatment in HNC pts (3-yr LRC FIT = 50%). Accrual time 12 months; minimum fup 24 months.
For the FIT group, a non-inferiority logrank test with a sample size of 100 subjects will achieve 81% power for concluding that LRC is not worse than 20% less than the reference of 50%; with 15% competing mortality or censoring, the power will drop to 77%.
For the VULNERABLE group, we accept a reduction of max 10% of the LRC in comparison with fit pts. So, a non-inferiority logrank test with a sample size of 200 subjects will achieve 85% power for concluding that LRC is not worse than 15% less than the reference of 40%; with 15% competing mortality or censoring, the power will drop to 81%.
Accrual time 12 months; minimum fup 24 months.
For the FRAIL subgroup, a binomial test for non-inferiority with a sample size of 80 subjects will achieve 92% power for concluding that the foreseen treatment intensity is not lower than 15% less than the reference of 85%; assuming a 20% mortality, the power will drop to 85%. Accrual time 12 months and fup of 6 months.

Number of centres

The trial will be proposed to 10 Italian Centres with a recognized expertise in HNC pts treatment, able to accrual the required sample in the expected timeframe.
Investigators' meetings and teleconferences will be conducted in order to assure homogeneity in the procedures of the study.

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