Neoadjuvant Carboplatin and Vinorelbine Followed by Chemoradiotherapy in Locally Advanced Head and Neck or Oesophageal Squamous Cell Carcinoma: A Phase II Study in Elderly Patients or Patients with Poor Performance Status

HARALABOS KOUSSIS[1], ANNAMARIA SCOLA[1], FRANCESCA BERGAMO[1], STEFANO TONELLO[2], UMBERTO BASSO[1], PARASKEVI KARAHONTZITIS[3], VANNA CHIARION-SILENI[1], LARA PASETTO[1], ALBERTO RUOL[4], LUCIO LOREGGIAN[5], ORNELLA LORA[5], RAFFAELE BOTTIN[6], GINO MARIONI[6], MARTIN DONACH[1] and ANTONIO JIRILLO[1]

Departments of [1]Medical Oncology and [5]Radiotherapy, Istituto Oncologico Veneto IRCCS; [2]Odontological Department and [4]Surgical Clinic Ospedale-Università Padova, Italy; [3]Radiotherapy Department, Metaxa Hospital, Athens, Greece, [6]Department of Medical and Surgical Specialties, Section of Otolaryngology, University of Padova, Italy

Abstract. *Background: The purpose of this study was to evaluate the efficacy and toxicity of neo-adjuvant carboplatin and vinorelbine followed by concomitant chemoradiotherapy in patients ≥70 years of age or with Karnofsky performance status (PS) 70-80, diagnosed with locally advanced head and neck (H&N) or oesophageal carcinoma. Patients and Methods: The treatment plan consisted of three courses of carboplatin AUC4 on day 1 and vinorelbine 25mg/m^2 on day 1 and 8, every 21 days, followed by chemoradiotherapy. Carboplatin 100 mg/m^2 was delivered weekly for the duration of the radiation therapy (70 Gy, 2 Gy/daily). Results: Thirty-five patients with an average age of 68 years (range 42-85, 16 patients ≥70 years) were treated. Twenty-seven patients (77.1%) responded to neo-adjuvant chemotherapy (2 complete and 25 partial responses). Haematological toxicity was grade 3-4 in 13 patients (37.2%), while gastrointestinal toxicity was grade 3-4 in 20 patients (57.1%). All the patients completed the chemoradiotherapy plan, with grade 4 mucositis plus febrile neutropenia in 3 patients (8.5%). Median time to progression (TTP) was 10.2 months, with 31.5% of patients being alive at two years. Conclusion: The regimen of neo-adjuvant carboplatin and vinorelbine followed by chemoradiotherapy is feasible and active in older (≥70 years) or low PS (Karnofsky 70-80) patients, although toxicity is not negligible and long-term outcome remains poor.*

Correspondence to: Dr. Haralabos Koussis, Department of Medical Oncology, Istituto Oncologico Veneto I.R.C.C.S., via Gattamelata 64, 35128 Padova, Italy. Tel: +39-049 8215931, Fax: +39-049 8215932, e-mail: drbabis@libero.it

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Head and neck (H&N) cancer currently accounts for 10% of malignant tumours in men and 4% in women worldwide, and mainly affects patients over 50 years of age. Concomitant chemoradiotherapy is the standard treatment for locally advanced, inoperable H&N cancer, with improved local control, time to progression (TTP) and overall survival (OS) (1). Unfortunately, despite optimal therapy, approximately 50-60% of these patients show local recurrence and 30% develop distant metastases (2, 3). Neo-adjuvant chemotherapy has been shown to preserve organ function and significantly reduced the incidence of distant metastases, but its efficacy in prolonging overall survival has not been demonstrated (4, 5).

Oesophageal cancer is a rarer disease and mainly arises in males (2-4 times more prevalent) and in patients over the age of 60. The optimal timing of multimodal treatment (chemotherapy, radiotherapy and/or surgery) is still unknown. There is no general agreement on the effect of neo-adjuvant treatments for oesophageal squamous cell carcinomas on patient survival (6, 7).

Both H&N and oesophageal cancer have the same aetiological causes (tobacco smoke and alcohol consumption), the same prevalent histology (squamous cell) and the same propensity for loco regional diffusion rather than distant spreading. A combination of cisplatin and 5-fluorouracil (5-FU) delivered in continuous infusion is the standard schedule for

patients with locally advanced or metastatic H&N and oesophageal cancer (2, 8). This regimen does not appear feasible for elderly or poor performance status (PS) patients because the intrinsic decline of renal function with age and the potential risks of the hyper-hydration required by cisplatin administration may contraindicate the use of this drug, and malnutrition, increased sensitivity of oral and gastro-intestinal mucosae to fluoropyrimidines and the frequent presence of cardiac comorbidities may exclude the continuous infusion of 5-FU.

Vinorelbine is active in H&N carcinoma (9), and its use has been validated in elderly patients with metastatic lung (10) or breast cancer (11, 12). Vinorelbine has been administered even to frail elderly patients with non-Hodkgin's lymphomas with manageable toxicity (13).

Due to its lower nephrotoxicity, carboplatin is usually the preferred platinum derivative to be used in elderly or poor PS patients, although a slight reduction in effectiveness has been demonstrated in lung cancer. Evidence of synergy with radiotherapy justifies its co-administration with radiation treatment, usually with a weekly schedule (14).

In this phase II study a neo-adjuvant combination of carboplatin and vinorelbine was used for the treatment of elderly or poor PS patients in order to reduce the potential renal, mucosal and cardiac toxicities of the standard regimen of cisplatin plus continuous infusion of 5-FU, followed by radiotherapy at radical doses concurrent with carboplatin.

Patients and Methods

Eligibility. Thirty-five consecutive patients were recruited. Eligible patients had a histological diagnosis of non-metastatic H&N or oesophageal squamous cell carcinoma, stage III or IV. The patients were required to have radiologically, endoscopically and/or clinically assessable disease. All the patients were ≥70 years and/or showed a Karnofsky PS of 70-80. Comorbidity of the elderly patients was evaluated according to the Cumulative Illness Rating Score-Geriatric (CIRS-G) (15). Exclusion criteria were: inadequate bone marrow reserve (white blood cells, WBC <3,000/μL; platelets, PLT <100.000/μL; haemoglobin, Hb <10 gr/dL); creatinine >2 x upper normal limit (UNL); total bilirubin >1.5 x UNL, aspartate aminotranferase, AST and alanine aminotransferase ALT >2.5 x UNL, alkaline phosphatase >2.5 x UNL; previous or current malignancies at other sites, with the exception of adequately treated "*in situ*" carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin and the presence of concomitant serious illness or medical condition including chronic obstructive lung disease, unstable cardiac disease despite treatment, myocardial infarction within 6 months prior to study entry, chronic gastro-intestinal disease with malnutrition and cognitive impairment.

All the patients signed a written consent form for the treatment and the start of the trial was communicated to the local Ethics Committee, according to standard procedures active in Italy in 1999.

Treatment plan

Chemotherapy. The treatment plan consisted of the administration of carboplatin (AUC 4) on day 1 and vinorelbine 25 mg/m^2 on days 1 and 8. Antagonists of 5-hydroxytryptamine (5-HT3) receptors were prescribed as antiemetics in association with 4 mg dexamethasone, intravenously. In the presence of neutrophils ≥1,500/μL and platelets ≥100, 000/μL chemotherapy was repeated every 21 days for 3 cycles. Granulocytic and erythropoietic growth factors were allowed in cases of severe myelodepression at the treating physician's discretion, but their prophylactic use in order to recycle chemotherapy in time was strongly discouraged. Dose reductions were permitted in cases of haematological toxicity ≥ grade 3 and non-haematological ≥ grade 2. The mean dose intensity was calculated for each patient (mg/m^2/week). Four weeks after the last course of chemotherapy, the chemoradiotherapy treatment was started. Carboplatin 100 mg/m^2 was administered weekly concomitantly with radiation therapy delivered at radical doses (70 Gy).

Radiotherapy. Radiotherapy was delivered by a linear accelerated 6 megavolt (LINAC 6 MV). The target volume varied according to tumour location and stage. Whenever possible, the therapy was planned from CT scan images at several different levels. For the patients with H&N cancer, the external beam radiotherapy (EBRT) programme consisted of a total dose of 70 Gy to the primary lesion delivered in 35 daily fractions of 2.0 Gy (5 days/week), with a 1 to 2 week interruption whenever required by the severity of mucositis. The total dose to the regional lymph nodes was set to 60 Gy.

For the patients with oesophageal cancer, the initial volume of EBRT included the primary lesion in the oesophagus as identified by endoscopic evaluation and CT-scan, with a 5 cm margin above and below and 2 cm laterally, comprising also paraoesophageal and regional lymph nodes. For the lesions of the upper thoracic oesophagus, the supraclavicular lymph nodes were also irradiated. For the lesions situated in the lower thoracic oesophagus, the lymph nodes of the left gastric artery and celiac trunk were irradiated. The final volume included the primary oesophageal lesions with 2 cm margins and all clinically or biopsy involved lymph nodes. The total transcutaneous radiation should have been 45 Gy and the spinal cord should not have received more than 45 Gy.

Patient evaluation. After histological diagnosis, all the patients underwent staging of disease by both endoscopy and CT-scan. Ecography was applied to study the regional lymph nodes whenever required. Haematology and biochemistry tests were performed before each cycle of chemotherapy and weekly during chemoradiotherapy in order to monitor haematological, renal and liver toxicity. All the patients underwent disease re-evaluation with the same modality applied at baseline after neo-adjuvant chemotherapy and then after completion of chemoradiotherapy. In the presence of either measurable or not measurable disease, the treatment was evaluated according to the WHO criteria. Toxicity was graded according to National Cancer Institute (NCI)-Common Toxicity Criteria version 2.0. (16).

In the H&N patients who achieved complete remission at the primary site (histologically or cytologically confirmed), neck dissection was performed in cases of disease persistence in the lymph nodes.

Study end-points. The primary objectives were to evaluate the feasibility, effectiveness and toxicity of a neo-adjuvant regimen of carboplatin plus vinorelbine followed by chemoradiotherapy in elderly and/or poor PS patients with locally advanced H&N or oesophageal cancer.

Table I. *Patient characteristics*.

Number	35
Male/female ratio	27/8
Age	
Median	68 years
Range	42-85 years
Elderly patients (>70 years)	16 (45.7%)
Karnofsky performance status	
Median	80
Range	70-100
Patients with PS 90-100	10 (28.5%)
Patients with PS 70-80	25 (71.4%)
Site of disease	
Oropharynx or hypopharynx	21
Larynx	4
Oesophagus	9
Neck lymph nodes	1
Stage of disease	
III	17
IV	18

Table II. *Response to neo-adjuvant chemotherapy.*

	Number (%)	
Response		
Complete (CR)	2/35 (5.7)	
Partial (PR)	25/35 (71.4)	
Overall (CR + PR)	27/35 (77.1)	
Response according to age		
Elderly	14/16 (87.5)	
Non-elderly	13/19 (57.8)	
		p=0.24
Response according to site of disease		
H&N cancer	22/26 (84.6%)	
Oesophageal cancer	6/9 (66.6%)	
		p=0.33

The secondary objectives were to evaluate the TTP and OS, and to compare elderly and not-elderly patients in terms of tumour response and toxicity.

Statistical analysis. Success was defined as evidence of an objective response (complete-CR or partial-PR) at the end of the neo-adjuvant chemotherapy. $p0$=0.2 was defined as the minimal success rate below which the treatment would be considered inactive and $p1$=0.4 as the success rate beyond which the treatment would be judged active. According to A'Hern (17), the study required 35 subjects to decide whether the proportion of responding patients (*i.e*. the success rate, p) was less than or equal to 0.2 or greater than or equal to 0.4. If the number of successes was 12 or more, the hypothesis that $p \leq 0.2$ was rejected with a target alfa error rate of 0.050 and an actual error rate of 0.034. If the number of successes was 11 or less, the hypothesis that $p \geq 0.4$ was rejected with a target alfa error rate of 0.2 and an actual error rate of 0.195.

For comparisons of activity and toxicity between subgroups, the patient numbers were compared by means of Chi-square test (with Fisher's exact correction for frequencies less then 5).

The TTP was calculated from the start of treatment to either progression of disease (at a local and/or metastatic site) or death from any cause. The OS was measured from the start of treatment to death from any cause. The status of patients lost at follow-up was checked by phone interviews or consultation with municipal registries. Kaplan-Meier estimations of TTP and OS were performed by means of Statistica software, version 6 (Statsoft, Inc., Tulsa, OK, USA), and subgroups were compared by log-rank test.

Results

Patient characteristics. Between August 1999 and September 2002, 35 patients (27 males and 8 females) affected by H&N or oesophageal cancer were enrolled. The population had an average age of 68 years (range 42-85 years) and a median PS of 80 (range 70-100). Sixteen of the patients were ≥ 70 years, 25 of the patients had a PS of 70-80 (Table I). No Grade 3 or 4 comorbidity according to the CIRS-G scale was present in the group of elderly patients at diagnosis, with the exception of one patient who presented with a grade 3 abdominal aortic aneurysm.

Treatment and dose intensity. A total of 99 courses (median 2.6 per patient; range 1-3) of neo-adjuvant carboplatin and vinorelbine were administered. Sixteen patients were treated with a full chemotherapy dose and 18 patients with a 25% dose reduction, without a significant difference of dose-intensity between elderly and non-elderly patients (p=0.22). All the patients completed the full programme of radiotherapy concomitantly with weekly carboplatin administration.

In the H&N group, seven patients underwent neck dissection for persistent lymph node disease after the completion of treatment with CR at the primary site.

Response. All the patients were evaluable for response (Table II). After neo-adjuvant chemotherapy 27 patients had responded (77.1% : 2 CR and 25 PR), therefore the protocol met the defined requirement for "success". Fourteen elderly patients (87.5%) and 13 non-elderly patients (57.8%) responded to neo-adjuvant chemotherapy (p=0.24). No significant difference in response was observed between H&N and oesophageal cancer (84.6 *vs*. 66.6%, p=0.33). Two H&N (7.7%) and no oesophageal cancer patients demonstrated CR. After completion of chemoradiotherapy, one more H&N patient demonstrated a response, giving an overall response rate of 80%.

Toxicity. All the patients were assessable for toxicity. During neo-adjuvant chemotherapy 3 patients had grade 3 haematological toxicity (8.6%), and 10 grade 4 (28.6%). The non-haematological toxicity included gastrointestinal

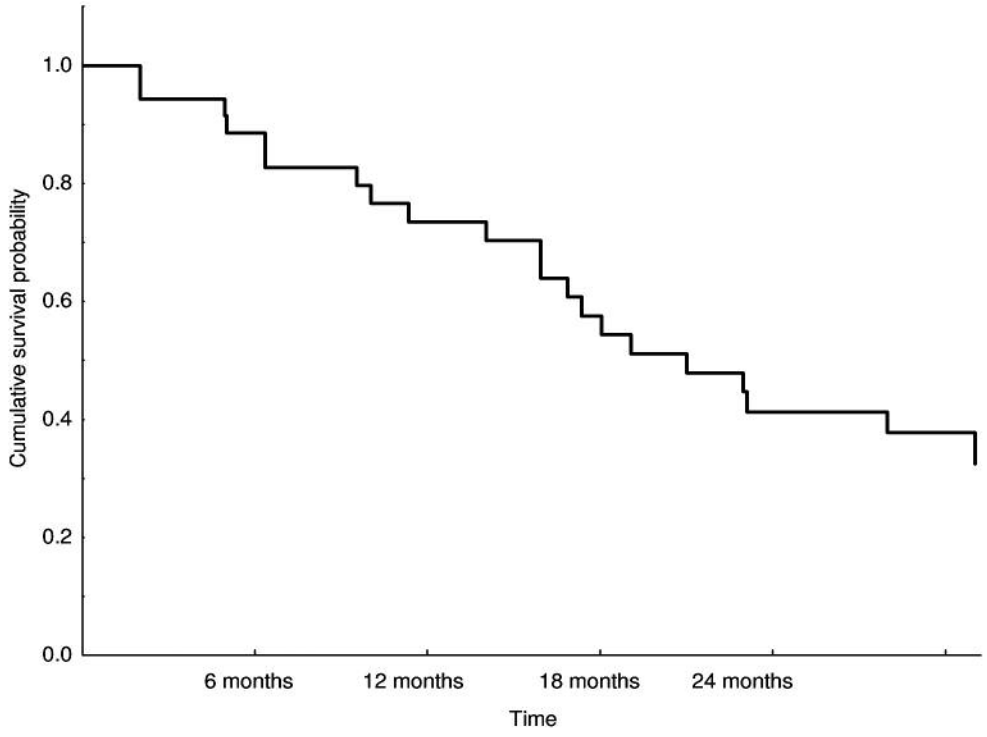

Figure 1. *Overall survival (23 events, 12 sensored patients).*

toxicity grade 3-4 in 20 patients (57.1%), consisting mainly of nausea/vomiting or constipation. Grade 4 mucositis was observed in only one patient. Haematological toxicity in the elderly was grade 3-4 in 5 patients (27.8%) and was not statistically different from the non-elderly patients (26.3%, p=0.74). No patient developed renal or cardiac toxicity.

During concomitant chemoradiotherapy three patients (8.5%) developed grade 4 mucositis and febrile neutropenia and were treated as in patients with broad-spectrum antibiotics and parenteral feeding. All of them recovered and were eventually able to complete the treatment. Three patients complained of relevant pain (1 retrosternal and 2 in the neck region), but electrocardiogram and troponine did not reveal any ischaemic cardiac lesion. In one patient osteonecrosis of the jaw was discovered. No toxic deaths were registered.

Progression and survival. After a median follow-up of 30.4 months, 29 patients had progressed and/or died, with a median TTP of 10.2 months. Twenty-three patients have died to date, with a median OS of 19.3 months and a 1- and 2-year survival rate of 73.4% and 41.5%, respectively (Figure 1). Currently, only 6 patients (17.1%) are still in complete remission. Age ≥70 years correlated with a longer TTP compared to younger patients with poor PS (16.2 *vs*. 8.1 months, p=0.045), but not with a different OS (18.3 *vs*. 17.6 months, p=0.30).

Discussion

The treatment of locally advanced H&N and oesophageal carcinoma in elderly patients or patients with poor PS is problematic since these patients have usually been excluded from clinical trials. Increased toxicity from anticancer treatments, relevant comorbidities and logistic limitations, as well as physicians' reluctance to propose a clinical trial to these patients are the main reasons for such under-representation (18). Due to the known difficulties of carrying out phase II studies in such categories of patients, both groups were enrolled in the trial with three cycles of neo-adjuvant carboplatin plus vinorelbine followed by chemoradiotherapy. The preservation of organ function was not an endpoint of this study, however, it could represent an undeniable advantage of this regimen.

To our knowledge, there are no other published trials with neoadjuvant chemotherapy followed by chemoradiotherapy in this subgroup of patients. Therefore, comparisons could only be made with similar therapies administered to patients with better PS and/or younger age. Seventy-seven percent of the patients in the present trial responded to neo-adjuvant chemotherapy, which was superior to the pre-fixed P1 level of 40%, but the number of CR was below 6%. In spite of a 25% dose reduction being applied to 51.4% of the patients, the toxicity of such treatment was relevant since almost one

third of the patients developed grade 4 haematological toxicity and more than a half had grade 3-4 gastrointestinal adverse events. Within the limitation of the small sample, age did not significantly influence the response rate or the toxicity rate. Overall, the response rate (84.6%) in the head and neck patients appeared comparable with published data on neo-adjuvant chemotherapy with cisplatin and 5-FU administered to patients of younger age and/or better PS (19), although the rate of CR was noticeably lower (7.7%). In fact, numerous studies conducted on H&N cancer have shown that the classical schedule of cisplatin plus continuous infusion of 5-FU may achieve a response rate ranging from 60% to 90%, with complete responses in 20% up to 50% of cases (5, 19, 20). Paccagnella *et al*. (4) reported a rate of CR and PR of 31% and 49%, respectively, after 4 courses of therapy, with haematological toxicity and mucositis in about 10% of cases and in 2 patients a miocardial infarction was documented. Lewin *et al*. (21) reported 48% CR and 23% PR achieved in patients evaluated after three neo-adjuvant cycles followed by radiotherapy alone with >10% of severe toxicity after chemotherapy and with 4 toxic deaths. Newer regimens with 3 agents seem to give even better rates, Posner *et al*. (22) added docetaxel to cisplatin and 5-FU and reported a CR rate of 40% along with 54% PR; grade 3 or 4 neutropenia was observed in 95% and febrile neutropenia in 19% of cases. Collevas *et al*. (20) reported a comparable response rate of 93% with 3 cycles of the same regimen with the addition of folinic acid, with grade 3-4 mucositis in 48% and nausea and vomiting in 15% of cases.

The different profile of toxicity led us to select carboplatin plus vinorelbine instead of the cisplatin-5-FU regimen, but randomized comparisons of carboplatin-based *vs*. cisplatin-based regimens in elderly patients are lacking. One of the advantages of this regimen was the avoidance of continuous infusion of 5-FU, which allowed the administration of chemotherapy on an out-patient basis, thus limiting costs. The multidimensional geriatric assessment should now become mandatory in the evaluation of elderly patients in order to accurately evaluate the potential risks of the two regimens according to the type of comorbidities and to all other functional, logistic and psychological geriatric issues which are assessed within this comprehensive and multidisciplinary evaluation (15). In our study 66.6% of patients with oesophageal cancer responded to neo-adjuvant chemotherapy. Kazuhiko *et al*. have reported a 33.3% response rate with 4 cycles of cisplatin and 5-FU every 4 weeks and grade 3-4 haematological toxicity was 27.5% (23). Chiarion-Sileni *et al*. (7) who administered 3 cycles of docetaxel, cisplatin and 5-FU to patients with a median age of 61 years (range 39-72) reported 49% clinical responses with 93% grade 3-4 haematological toxicity. Our data suggested that oesophageal cancer is moderately chemosensitive even in the advanced age.

Other studies of concomitant chemoradiotherapy have reported higher rates of toxicity than the present study, especially pharyngeal mucositis or haematological toxicity which were present in up to 80% of cases (24, 25). Notwithstanding the age and PS of our study population, toxicity levels of chemoradiotherapy were therefore in line with other studies and may be considered acceptable.

In conclusion, even though the CR rate was very low, the majority of patients responded with a median time of disease control of 10 months and overall survival exceeding 19 months. Therefore, this regimen may be considered as a reasonable palliation for elderly or poor PS patients with inoperable H&N or oesophageal cancer. Since the haematological and gastro-intestinal toxicity were rather pronounced, active monitoring of patients throughout the therapeutic sequence is strongly recommended.

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