# Efficacy and safety of vinorelbine in heavily pretreated recurrent/metastatic head and neck squamous cell carcinoma patients

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# EFFICACY AND SAFETY OF VINORELBINE IN HEAVILY PRETREATED RECURRENT/METASTATIC HEAD AND NECK SQUAMOUS CELL CARCINOMA PATIENTS

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**Running title:** Vinorelbine in head and neck cancer patients.

**ABSTRACT**

The objective of this study was to evaluate the efficacy and tolerance of vinorelbine as a single agent in the treatment of recurrent/metastatic head and neck squamous cell carcinoma. Patients were treated with oral or intra venous vinorelbine according to pluridisciplinary tumor board's decision. Efficacy and safety outcomes were analyzed retrospectively. Twenty-three patients were included in the study. Sixteen patients (69%) had received at least two previous lines of chemotherapy. The disease control rate was 19%. The median progression-free survival was 2,6 months and the median overall survival was 3,4 months. The rate of grade 3-4 side effect was low (13%). Only one patient discontinued treatment because of side effects. Vinorelbine seems to be a well-tolerated regimen in heavily pretreated patients. However, this regimen does not seem to be efficient enough to be recommended.

**Keywords:** head and neck cancer; vinorelbine; recurrent; metastatic; chemotherapy.

## Introduction

Head and neck squamous cell carcinoma (HNSCC) is one of the leading causes of cancer-related mortality in the Western world. The GLOBOCAN estimates there has been 513 000 new cases in 2012 worldwide.[1] In France, HNSCC's incidence was of 14 638 new cases in 2012 and mortality was of 4098 cases.[2] After the frontline locoregional treatment based on surgery and chemoradiotherapy, 50% of patients present a relapse.[3] In most cases, this relapse is non curable with surgery or radiation therapy. Chemotherapy is then the only therapeutic option used in a palliative intent. Common used drugs are platinum, docetaxel, paclitaxel, 5-fluorouracil (5-FU), and methotrexate. The standard first-line treatment for inoperable recurrent or metastatic HNSCC is platinum and 5FU combined with cetuximab.[4] With this regimen, median overall survival reaches 10 months. The only validated second-line chemotherapy is methotrexate with a poor response rate.[5] In platinium refractory patients, median overall survival has been estimated to 56 days with best supportive care.[6] All efforts should be made to improve the prognosis of these patients.

Vinorelbine is a cytostatic drug part of the vinca alkaloid family. Its anti-mitotic activity is caused by inhibition of microtubule polymerization during mitosis. Vinorelbine has been used in lung cancer and breast cancer for many years.[7,8] It has been previously evaluated as first line in patients with recurrent and/or metastatic HNSCC with a response rate of 16%.[9] Combined with other drugs, vinorelbine has a modest effect in HNSCC patients.[10,11,12] It could be interesting to use it as a monotherapy in patients non eligible for conventional treatment because of the comorbidities or numerous previous lines of chemotherapy.

We have retrospectively reviewed efficacy and tolerance of vinorelbine as monotherapy in HNSCC patients with recurrent or metastatic disease pre-treated with at least one line of chemotherapy.

## Patients and methods

### *Inclusion criteria*

We included in this study all patients treated with vinorelbine in our institution for a non resectable recurrent or metastatic squamous cell carcinoma of the head and neck between January 2006 and July 2013. Patients were eligible if they were 18 years of age or older and had pathologically confirmed recurrent or metastatic HNSCC. Other inclusion criteria included ineligibility for local therapy. Their medical charts were retrospectively reviewed.

### *Treatment*

Patients were treated with vinorelbine *per os* at a dose of 60 mg/m² on D1, D8 and D15 with D1=D28. If the hematological tolerance was good, the dose was increased to 90 mg/m² on D1, D8 and D15 after the third cycle of treatment. For patients unable to swallow, vinorelbine was administered IV at a dose of 25 mg/m² on D1, D8 and D15. Each administration of vinorelbine was preceded by an intake of ondansetron 8 mg half an hour before. Treatment was continued until progression or unacceptable toxicity. Before each new cycle, patients had a physical examination to evaluate tolerance and efficacy of treatment. They had a blood count every week.

### *Assessment of safety and efficacy*

Acute toxicity was evaluated by the clinician and graded at each cycle of chemotherapy according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Tumor response was assessed by physical examination at every cycle and by computed tomography (CT) or magnetic resonance imaging (MRI) in all patients using RECIST (Response Evaluation Criteria in Solid Tumors) 3 months after the start of vinorelbine and then at 3-month intervals.

*Statistical analysis*

The endpoints assessed were response to chemotherapy, progression free survival (PFS), overall survival (OS), and acute toxicity. The Kaplan-Meier method was used to estimate the PFS and OS. PFS was calculated from the first day of chemotherapy initiation until the date of tumor progression or death. OS was calculated from the first day of chemotherapy initiation until the date of death. Analyses were performed with Statview v5 software.

## Results

*Patient characteristics*

From January 2006 through July 2013, 23 patients received vinorelbine for recurrent or metastatic HNSCC at our institution. The initial characteristics of the 23 patients analyzed in this study are reported in Table 1.

The median delay of relapse was 12.3 months (range: 5-103 months), with 13 locoregional recurrences (57%), seven metastatic recurrences (30%) and three locoregional and metastatic recurrences (13%). Patients with metastatic relapse presented mainly with lung metastasis (70%).

Two patients (9%) received vinorelbine as frontline for the treatment of their relapse, five patients (22%) received one line of chemotherapy prior to vinorelbine, 11 patients (47%) received two lines of chemotherapy prior to vinorelbine and five patients (22%) received three lines of chemotherapy prior to vinorelbine. Sixteen patients (70%) received cisplatin prior to vinorelbine, 19 patients (83%) cetuximab, 19 patients (83%) docetaxel, one (4%) methotrexate, and one (4%) gemcitabine plus oxaliplatin (Table 2).

*Treatment delivery and safety*

Patients received a mean of 2.2 cycles (range: 1-7). Vinorelbine was mainly administered *per os* (78% of patients). Dose reduction was not needed.

All patients were assessable for tolerance. Treatment was stopped prematurely in one patient after two cycles because of grade 3 asthenia.

Acute toxicities are summarized in Table 3. Anemia, diarrhea, and constipation were the most frequent side effects. The overall incidence of severe (grade 3-4) acute toxicity was low with two cases of grade 3 neutropenia (9%) and one case of grade 3 asthenia (4%). There was no case of febrile neutropenia. There was no death related to treatment.

*Efficacy and survival*

The median follow-up time was 3.4 months (range: 0.1-14.1 months).

Response was assessable in 16 patients. In seven patients, the response was not assessed because they received only one cycle of vinorelbine. No objective tumor response has been observed. Three patients (19%) had disease stabilization. All of them had a tumor originally located in the oropharynx. Their HPV status was unknown. Among the seven patients who received at least three cycles of vinorelbine, three had tumor stabilization (43%).

All patients have been included in survival analysis. At the time of analysis, there have been 22 deaths and 23 disease progression. The median PFS was 2.6 months and the median OS was 3.4 months (Figures 1 and 2). The 1-year actuarial PFS and OS rates were 0% and 4% (95% CI, 0-8%), respectively.

Eight patients have been able to receive another line of chemotherapy after vinorelbine: three patients received methotrexate, two carboplatine, two cetuximab, and one capecitabine. Other patients received best supportive care only.

**Discussion**

De nos jours, le standard de traitement des cancers ORL récurrents ou métastatiques est la combinaison de platine, 5-FU et cetuximab suivie d'un traitement de maintenance par cetuximab. En effet, dans l'étude EXTREME,[4] l'adjonction de cetuximab au 5FU et au platine a permis d'obtenir un taux de réponse de 36%, une augmentation de la PFS de 3,3 à 5,6 mois et de la survie de 7,4 à 10,1 mois. Cependant, la triple association était associée à un risque plus élevé de sepsis grave (9 vs 1 patients, p=0,02) et à une toxicité cutanée de grade 3-4 de 9% (vs <1%, p<0,001). Les patients inclus étaient en bon état général (indice de Karnofsky ≥ 80 chez plus de 88% des patients) et n'avaient pas de défaillance d'organes. De ce fait, beaucoup de patients ne sont pas éligibles à ce protocole et d'autres stratégies thérapeutiques doivent donc être envisagées. Il apparaît ainsi 2 groupes de patients. Le premier correspond aux patients en bon état général, en 1ère ligne métastatique ou en rechute locorégionale, pouvant bénéficier du traitement optimal cité ci-dessus. Le 2ème groupe de patients comprend les cas de récidive après traitement à base de platine, les patients en moins bon état général ou présentant des comorbidités rendant impossible la réalisation de cette association de traitement. Pour ceux-là, d'autres options thérapeutique doivent être envisagées.

De nombreuses molécules ont été testées en monothérapie ou en association, comme le méthotrexate, le carboplatine, le docetaxel, le paclitaxel, la capecitabine, le pemetrexed ou le cetuximab, avec des taux de réponse variant entre 10 et 50%.[5,13,14,15,16]

L'utilisation d'agents en monothérapie peut être utile chez les patients fragiles, dénutris, présentant des comorbidités, des défaillances d'organe ou ayant reçu plusieurs lignes de traitement. Classiquement, le méthotrexate est un agent de 2ème ligne de choix après utilisation des sels de platine du fait de son bon profil de tolérance. Malgré un taux de réponse faible (8 à 16%), il permet d'observer une médiane de survie de l'ordre de 6 mois.[5,17] Les taxanes utilisés en monothérapie chez les patients réfractaires au platine ont une efficacité modérée avec des taux de réponse de 10% (docetaxel) à 20% (paclitaxel).[18, 19] La capecitabine

permet d'obtenir un taux de réponse de 17% chez des patients ayant également déjà reçus des platines.[20]

La vinorelbine est un autre agent cytotoxique. Son efficacité en monothérapie a déjà été étudiée dans les cancers ORL récidivants ou métastatiques. En effet, l'étude de Degardin M. et al de l'EORTC-ECSG en 1998 retrouvait un taux de réponse de 16% chez des patients en situation de rechute ou métastatique non traités précédemment avec une médiane de survie sans progression de 3 mois, une survie médiane de 8 mois et une durée médiane de réponse de 4,7 mois suggérant une activité intéressante de la molécule dans ce type de cancers.[9]

Au vu de ces résultats, il nous a semblé intéressant d'utiliser cette molécule en 2ème ligne ou plus chez des patients présentant une rechute locorégionale ou métastatique.

Notre étude retrouve un taux de réponse nul mais un temps jusqu'à progression du même ordre de 2,6 mois. Bien que la comparaison entre les études soit délicate, on note cependant que la médiane de survie est plus faible dans notre étude (3,4 mois vs 8 mois). Cette différence peut être attribuée au faible nombre de patients inclus (n=23), et au fait que nos patients aient été plus lourdement traités antérieurement (69% des patients avaient reçus au moins 2 lignes de chimiothérapie avant la vinorelbine et plus de 70% de nos patients avaient bénéficié d'une chimiothérapie à base de platine alors qu'aucun patient n'avait reçu de chimiothérapie hormis néo-adjuvante ou adjuvante dans l'étude de l'EORTC). Ce traitement était par ailleurs bien toléré et 8 patients (35%) ont pu recevoir une autre ligne de chimiothérapie après la vinorelbine.

L'efficacité de la vinorelbine apparaît moindre que celle d'autres agents cytotoxiques en monothérapie chez les patients présentant un cancer ORL récidivant ou métastatique. Son usage ne peut donc pas être recommandé dans cette situation.

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**Legends of figures**

**Figure 1 – Kaplan-Meier estimates of progression free survival for all patients.**

**Figure 2 – Kaplan-Meier estimates of overall survival for all patients.**

**Figure 1.**

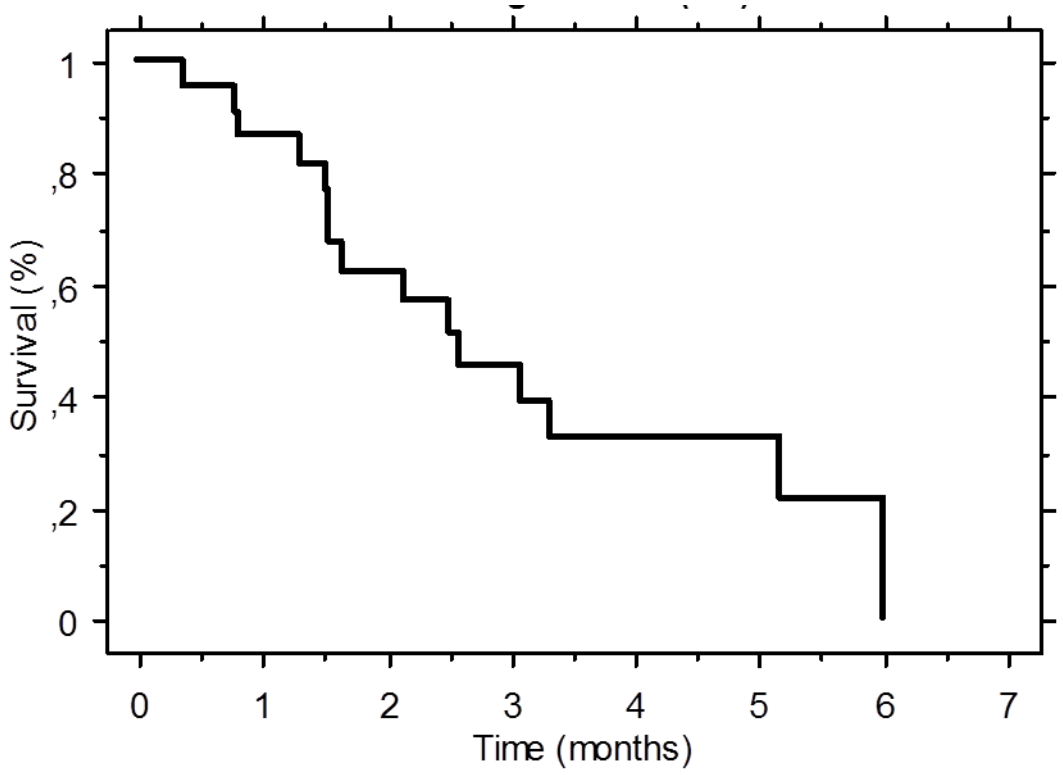
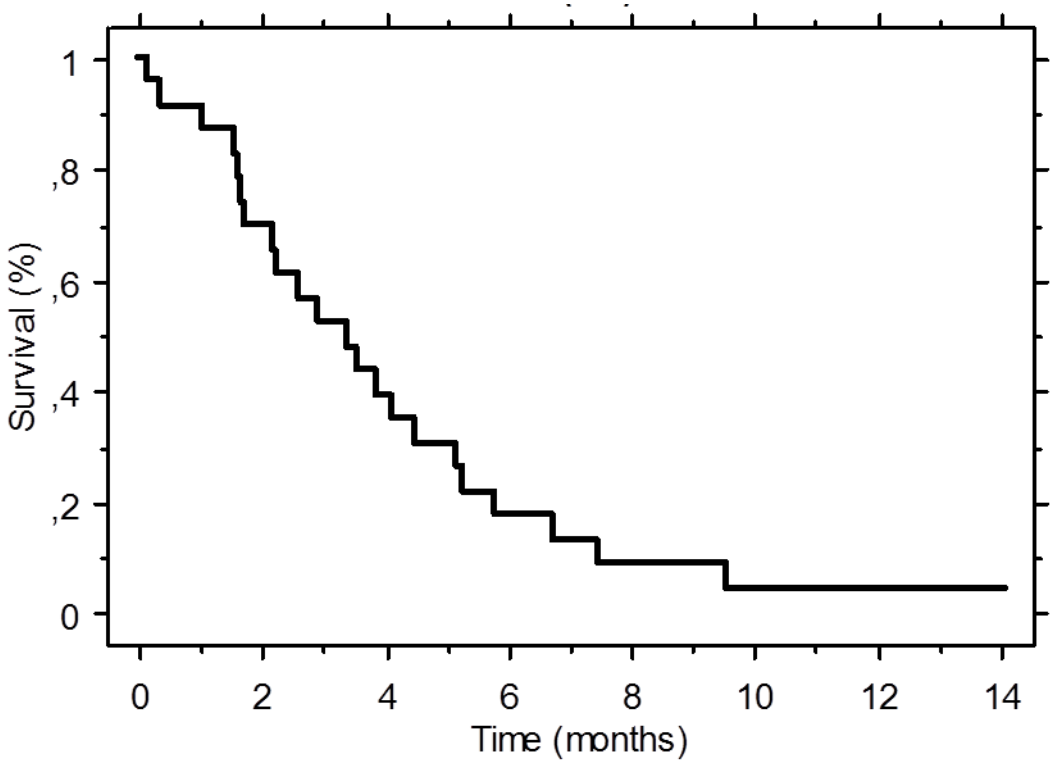


**Figure 2.**



**Tables**

**Table 1 – Initial characteristics of patients.**

| **Characteristics** | **Total** n=23 |
|---|---|
| **Age** (years old) | |
| median | 61 |
| range | 34-83 |
| **Sex** (n ; %) | |
| male | 17 (74) |
| female | 6 (26) |
| **Initial T stage** (n ; %) | |
| T1 | 3 (13) |
| T2 | 5 (22) |
| T3 | 8 (35) |
| T4 | 7 (30) |
| **Initial N stage** (n ; %) | |
| N0 | 6 (26) |
| N1 | 4 (17) |
| N2a | 2 (9) |
| N2b | 2 (9) |
| N2c | 3 (13) |
| N3 | 6 (26) |
| **Tumor location** (n ; %) | |
| oral cavity | 4 (17) |

| | |
|---|---|
| oropharynx | 10 (44) |
| larynx | 3 (13) |
| hypopharynx | 5 (22) |
| nasopharynx | 1 (4) |
| **Initial treatment** (n ; %) | |
| Surgery | 2 (9) |
| Surgery followed by RT | 2 (9) |
| ICT followed by surgery | 2 (9) |
| ICT followed by surgery and RT | 7 (30) |
| RT | 3 (13) |
| ICT followed by RT | 7 (30) |

Abbreviations: n, number of patients; T, tumor; N, lymphe node; RT, radiation therapy; ICT, induction chemotherapy.

**Table 2 - Different lines of chemotherapy prior vinorelbine for recurrent or metastatic HNSCC.**

| **Chemotherapy** | **1st line** (n) | **2nd line** (n) | **3rd line** (n) |
|---|---|---|---|
| **Cisplatin** | 11 | 4 | 1 |
| **Cetuximab** | 6 | 10 | 3 |

Abbreviations: n, number of patients

**Table 3 - Toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.**

| **Toxicity** | **Grade 1-2** | **Grade 3-4** |
|---|---|---|
| **Hematological** (n ;%) | | |
| Anemia | 5 (22) | 0 |
| Neutropenia | 2 (9) | 2 (9) |
| Thrombopenia | 0 | 0 |
| **Gastro-intestinal** (n ;%) | | |
| Nausea - vomiting | 1 (4) | 0 |
| Diarrhea | 5 (22) | 0 |
| Constipation | 3 (13) | 0 |
| **Other** (n ;%) | | |
| Hepatic cytolysis | 1 (4) | 0 |
| Mucositis | 1 (4) | 0 |
| Asthenia | 1 (4) | 1 (4) |

Abbreviations: n, number of patients