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Cetuximab Pharmacokinetics Influences Overall Survival in Patients With Head and Neck Cancer

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Background: A retrospective study was conducted to analyze interindividual variability of cetuximab pharmacokinetics and its influence on survival (progression-free survival and overall survival [OS]) in a cohort of head and neck squamous cell carcinoma (HNSCC).

Methods: Thirty-four patients received cetuximab as an infusion loading dose of 400 mg/m² followed by weekly infusions of 250 mg/m². Twenty-one patients had locally advanced HNSCC, and 13 had metastatic/recurrent HNSCC. Cetuximab concentrations were measured by the enzyme-linked immunosorbent assay, and its pharmacokinetics was analyzed by a population approach. Survivals were analyzed with the log-rank test.

Results: Cetuximab pharmacokinetics was best described using a 2-compartment model with both first-order and saturable (zero-order) eliminations. Estimated pharmacokinetic parameters (%CV) were central volume of distribution $V_1 = 3.18$ L (6%), peripheral volume of distribution $V_2 = 5.4$ L (42%), elimination clearance $CL = 0.57$ L/d (31%), distribution clearance $Q = 0.64$ L/d, and zero-order elimination rate $k_0 = 6.72$ mg/d (29%). Both V_1 and V_2 increased with the body surface area. Adjunction of chemotherapy reduced CL and increased k_0 . OS was inversely related with cetuximab global clearance ($P = 0.007$) and was higher in patients with severe radiation dermatitis ($P = 0.005$).

Conclusions: Cetuximab pharmacokinetics in patients with HNSCC can be described using a 2-compartment model combining linear and nonlinear mechanisms of elimination. OS is associated with both cetuximab global clearance and severe radiation dermatitis.

Key Words: head and neck cancer, cetuximab, pharmacokinetics, toxicity, survival analysis

INTRODUCTION

Cetuximab is a chimeric human–mouse immunoglobulin G1 kappa monoclonal antibody directed against the extracellular ligand-binding domain of the epidermal growth factor

receptor (EGFR). It is approved in locally advanced head and neck squamous cell carcinoma (HNSCC) in association with radiotherapy^{1,2} and in recurrent or metastatic HNSCC in association with chemotherapy.³ It is also approved in metastatic colorectal cancer alone or in combination with chemotherapy for RAS mutations.^{4–10} Adjunction of cetuximab for the treatment of these cancers improves overall survival (OS) and/or progression-free survival (PFS).^{1–3}

Part of the interindividual variability in response to cetuximab may be explained by the interindividual variability in its pharmacokinetics, as reported for all monoclonal antibodies.^{11,12} Fracasso et al¹³ observed, in patients treated for different types of carcinomas, that responders had higher trough cetuximab serum concentrations than those of nonresponders. The first population pharmacokinetic study of cetuximab was reported by Dirks et al¹⁴ in patients with HNSCC. The authors described all cetuximab elimination as nonlinear, using a Michaelis–Menten type equation. Nonparametric analyses of cetuximab pharmacokinetics were also reported,^{15,16} but this approach does not allow an analysis of sources of interindividual variability. In metastatic colorectal cancer, cetuximab pharmacokinetics was described using a model combining linear and nonlinear eliminations,¹⁷ and its global clearance was found to be negatively related to PFS. Another predictive factor is the occurrence of dermatological adverse side effects. Relationships between skin toxicity (rash or folliculitis) of anti-EGFR monoclonal antibody and cancer response or patient survival were indeed reported.²

The aims of this study were to analyze both cetuximab pharmacokinetics and cetuximab skin toxicity as predictors of survival in a cohort of patients with HNSCC treated by this monoclonal antibody alone or combined with radiotherapy and/or chemotherapy.

MATERIALS AND METHODS

Patients and Treatments

A total of 34 consecutive patients with histologically confirmed stage II to IV HNSCC treated with cetuximab were retrospectively analyzed. Patients had locally advanced head and neck squamous cell carcinoma (LAHNSCC, $N = 21$) or metastatic/recurrent head and neck squamous cell carcinoma (MHNSCC, $N = 13$). Cetuximab was given at a loading dose of 400 mg/m² followed by weekly infusions of 250 mg/m². It was combined with radiotherapy ($N = 21$, plus chemotherapy for 1 patient), with platinum-based chemotherapy ($N = 10$), or was administered alone ($N = 3$).

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Cetuximab Concentration Measurements

As part of routine therapeutic drug monitoring of patients treated with cetuximab for HNSCC, blood samples were collected to measure cetuximab serum concentrations.^{13,17,18} Individual results were sent to the prescriber and were discussed during clinical-biological interdisciplinary rounds. The samples were therefore not drawn specifically for this study, which was performed retrospectively. At each infusion, blood samples were collected to measure cetuximab serum concentrations before and 2 hours after the end of the infusion. Cetuximab serum concentrations were measured using a validated enzyme-linked immunosorbent assay technique.¹⁸ Briefly, the validation required calibrators and quality controls bias (CV%) below 20%. Limit of detection was 0.012 mg/L, and lower limit of quantitation (LLOQ) was 0.75 mg/L.

Cetuximab Pharmacokinetic Analysis

Cetuximab serum concentrations were analyzed by the population pharmacokinetic approach using the nonlinear mixed-effect modeling software MONOLIX 4.3.2.^{19,20} One- and two-compartment models with first-order and/or saturable elimination from the central compartment were tested. To describe the saturable component of the elimination of cetuximab, two approaches were compared: a Michaelis–Menten equation with maximum elimination rate (V_{max}) and Michaelis–Menten constant (K_m), and a simple zero-order elimination described by constant k_0 . The other pharmacokinetic parameters were central (V_1 , with concentration C_1) and peripheral (V_2 , with concentration C_2) volumes of distribution, and systemic (CL) and distribution (Q) clearances. All models were internally validated using goodness-of-fit and residual plots and objective function values. Discrimination between hierarchical models was based on the likelihood ratio test, for which a change in objective function value >3.84 was considered statistically significant ($\alpha < 0.05$). The final model included random effects for all pharmacokinetic parameters except Q. A proportional error model gave the best description of residuals. Tested continuous covariates were: age, weight (WT), body surface area (BSA), approximated pretreatment volume ($4/3\pi \cdot r_1 \cdot r_2 \cdot r_3$), and surface ($3 \cdot \text{volume}/4\pi$)^{1/3} of tumors based on measured disease dimensions. Continuous covariates were centered on their median value. Tested categorical covariates were sex and treatment (chemotherapy or not). Radiotherapy was not tested because, except for 1 patient, patients who received radiotherapy did not receive chemotherapy. The covariate model was built using a stepwise forward addition/backward deletion modeling approach.²¹

Because only time-independent prognostic factors can be included in a survival model and because our pharmacokinetic model combines concentration-dependent and concentration-independent elimination rates, we used a global pharmacokinetic parameter to quantify cetuximab elimination. The cumulative area under the cetuximab concentration versus time curve (cumulative AUC) at the time of the event (progression, death, or censoring) was computed using estimated model parameters, as described previously.¹⁷ Cetuximab global clearance at the time of the event was calculated by dividing the cumulative cetuximab dose by cumulative AUC.

Clinical Endpoints

Time to progression was calculated as the delay between the first day of cetuximab infusion and the first observation of disease progression or death from any cause. If a patient had not progressed or died, time to progression was censored at the time of last known follow-up visit.

OS was defined as the time from first cetuximab infusion to death. PFS was defined as the time from first cetuximab infusion to recurrence (local, lymph nodes, metastasis) or disease progression according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Toxicities (radiation dermatitis, mucositis, and folliculitis) were graded for severity from grades 1 to 5, according to the CTCAE v4.02 scale (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Cetuximab-related toxicities were analyzed each week during radiotherapy in curative intent (and its potential impact) only in the LAHNSCC population (N = 21). To analyze the association of radiation dermatitis and mucositis toxicities with survival, low skin and mucositis toxicities were defined as grades 0 to 2 and severe as grades 3 to 4. To analyze the association of folliculitis toxicity with survival, low toxicities were defined as grades 0 to 1 and severe as grades 2 to 3.

Survival Analysis

PFS and OS (and their 95% CI) were estimated using the Kaplan–Meier method and compared with the log-rank test. The influence of potential prognostic factors on hazard ratios was tested using the likelihood ratio with and without the prognostic factor. The following factors were tested: age, cetuximab global clearance (and its value below or above the median value), chemotherapy, and cetuximab-related toxicities.

Local Ethics Committee Approval

For retrospective analysis as performed in this study, a specific ethics approval is not necessary.

RESULTS

Patients' Description and Toxicities

A total of 34 consecutive patients with HNSCC were analyzed (Table 1). Two patients were scored as stage II and the others as stages III or IV. All female patients were LAHNSCC.

Cetuximab was administered alone to 3 patients, combined with radiotherapy in 21 patients (median number of doses was seven during radiotherapy), and combined with chemotherapy alone in 10 patients (details of treatment are reported in Table 1). Toxicities are reported in Table 2.

Cetuximab Pharmacokinetic Analysis

A total of 544 cetuximab serum concentrations (mean of 16 samples per patient; range 2–76) were available. The 2-compartment model with both first- and zero-order eliminations gave better results than that with only Michaelis–Menten elimination. The model was able to describe the concentrations of cetuximab satisfactorily. Estimated pharmacokinetic parameters are displayed in Table 3. Volumes of distribution of the central (V_1) and the peripheral (V_2) compartments increased

TABLE 1. Baseline Characteristics of Cohort Patients

	Total Cohort (N = 34)	LAHNSCC Population (N = 21)	MHNSCC Population (N = 13)
Age, yrs			
Mean	61	61	61
Range	40–84	40–84	49–74
Sex, n (%)			
Male	31 (91.2)	18 (85.7)	13 (100)
Female	3 (8.8)	3 (14.3)	0 (0)
Karnofsky performance status, n (%)			
100	18 (53.0)	12 (57.1)	6 (46.1)
90	10 (29.4)	7 (33.3)	3 (23.1)
80	3 (8.8)	1 (4.8)	2 (15.4)
70	3 (8.8)	1 (4.8)	2 (15.4)
Mean	92.6	94.3	90
Primary tumor site, n (%)			
Oral cavity	3 (8.8)	1 (4.8)	2 (15.4)
Oropharynx	18 (53.0)	12 (57.1)	6 (46.1)
Hypopharynx	7 (20.6)	5 (23.8)	2 (15.4)
Larynx	3 (8.8)	2 (9.5)	1 (7.7)
Unknown primary	1 (2.9)	1 (4.8)	0
Cutaneous primary	2 (5.9)	0	2 (15.4)
Stage of primary tumor T, n (%)			
Tx	1 (2.9)	1 (4.8)	0
T1	5 (14.7)	1 (4.8)	4 (30.75)
T2	12 (35.3)	8 (38.1)	4 (30.75)
T3	10 (29.4)	8 (38.1)	2 (15.4)
T4	6 (17.7)	3 (14.2)	3 (23.1)
Node stage (N), n (%)			
N0	9 (26.45)	5 (23.8)	4 (30.75)
N1	7 (20.6)	5 (23.8)	2 (15.4)
N2a	2 (5.9)	2 (9.5)	0
N2b	9 (26.45)	5 (23.8)	4 (30.75)
N2c	5 (14.7)	3 (14.2)	2 (15.4)
N3	2 (5.9)	1 (4.9)	1 (7.7)
Treatments			
Radiotherapy	21	21	0
Cetuximab alone	3	0	3*
Chemotherapy	11	1	10†

*One patient for larynx cancer recurrence after chemotherapy failure, 1 patient for an oropharynx progression cancer after chemoradiation, and 1 patient for a progressive cutaneous cancer.

†Seven patients received the validated EXTREME regimen or equivalent³ with platinum-based chemotherapy plus fluorouracil, 1 patient received carboplatin plus fluorouracil (and radiotherapy in a protocol study—the only nonmetastatic patient receiving chemotherapy), 1 patient received carboplatin only (unfit patient), and 1 patient received cisplatin plus docetaxel (in a protocol study).

with BSA. First-order elimination (CL) of cetuximab was 1.6 times lower, and the saturated elimination rate (k_0) was 3.3 times higher in patients cotreated with chemotherapy. Other

TABLE 2. Graded Toxicities in LAHNSCC Treated With Radiotherapy (N = 21)

	Dermatitis	Mucositis	Folliculitis
Grades			
0	2	2	5
1	3	1	4
2	3	6	10
3	11	11	2
4	2	1	0
	Low = 8	Low = 9	Low = 9
	Severe = 13	Severe = 12	Severe = 12

tested covariates did not significantly influence cetuximab pharmacokinetics.

PFS and OS Analysis

Median PFS of the overall cohort of 34 patients was 11.56 months (95% CI, 6.18 to not reached (NR) months). The PFS of patients with MHNSCC and those with LAHNSCC was not significantly different ($P = 0.09$, log-rank test). In the overall cohort of 34 patients, PFS was longer in patients with cetuximab global clearance below the median value of 0.747 L/d (14.1 months, 95% CI, 7 to NR months) than in the other patients (11.6 months, 95% CI, 3.9 to NR months) ($P = 0.037$, Fig. 1). The association between cutaneous toxicity and PFS was analyzed in the 21 patients with LAHNSCC treated in curative intent with radiotherapy. Neither radiation dermatitis ($P = 0.251$) nor mucositis ($P = 0.857$)

TABLE 3. Estimated Cetuximab Pharmacokinetic Parameters

Parameter	Standard Error	Relative Standard Error* (%)	P	
V_1, L	3.18	0.09	3	
$CL, L/d$	0.57	0.07	12	
V_2, L	5.40	0.82	15	
$Q, L/d$	0.64	0.09	15	
$k_0, mg/d$	6.72	3.70	56	
$\beta_{V1}(BSA)$	1.28	0.26	21	0.000012
$\beta_{V2}(BSA)$	5.54	1.4	25	0.00063
$\beta_{k0}(TTT)$	1.2	0.59	49	0.04
$\beta_{CL}(TTT)$	-0.45	0.25	55	0.037
ω^2_{V1}	0.06	0.05	78	
ω^2_{CL}	0.30	0.05	17	
ω^2_{V2}	0.41	0.15	38	
ω^2_Q	—	—	—	
ω^2_{k0}	0.28	0.13	45	
σ^2_{prop}	0.32	0.01	3	

*(% r.s.e: (standard error/parameter value) \times 100.

β , influence of the covariate on pharmacokinetic parameter; σ , residual standard deviation; ω , interindividual standard deviation of pharmacokinetic parameter distributions; CL and Q, respectively, elimination and distribution clearances; k_0 , zero-order elimination; TTT, treatment = chemotherapy; V_1 and V_2 , respectively, central and peripheral volumes of distribution.

or folliculitis ($P = 0.242$) toxicities were significantly associated with PFS. Median OS of the overall cohort of 34 patients was 12.4 months (95% CI, 9.3 to 21.1 months).

The OS of patients MHNSSC and LAHNSSC was not significantly different ($P = 0.125$, log-rank test). In the overall cohort of 34 patients, OS (Fig. 2) was longer in patients with cetuximab global clearance below the median value (16.56 months, 95% CI, 12.35–55.7 months) than in the other patients (6.34 months, 95% CI, 3.88 to NR months) ($P = 0.007$).

Patients with LAHNSSC who developed severe radiation dermatitis toxicity (grade more than 3) had a longer OS than that of the other patients ($P = 0.005$, Fig. 3). No association was observed for mucositis ($P = 0.221$) or folliculitis ($P = 0.227$).

DISCUSSION

To our knowledge, this is the first study reporting the influence of cetuximab pharmacokinetics on OS in patients with HNSCC. Individual exposure to cetuximab was estimated by a population pharmacokinetic approach using a 2-compartment model with both first-order and saturable (zero-order) elimination. Pharmacokinetic parameters were estimated accurately (relative standard error ranging from x to y), which therefore provided accurate estimations of both AUC and cetuximab global clearance. Survival, as assessed by PFS and OS, was significantly associated with cetuximab global clearance. A population pharmacokinetic study of cetuximab in patients with HNSCC was previously reported by Dirks et al.¹⁴ The authors used a model describing all cetuximab elimination as nonlinear, using a Michaelis–Menten equation. More recently, cetuximab pharmacokinetics in metastatic colorectal cancer was described using a model combining linear and nonlinear eliminations. The

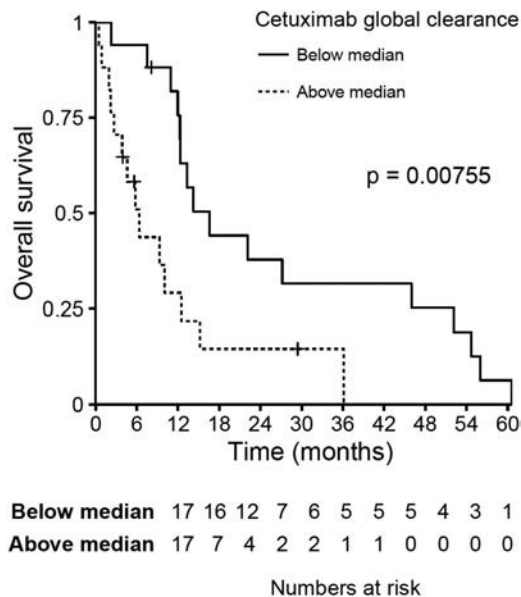


FIGURE 2. Kaplan–Meier curves of OS according to cetuximab global clearance in all patients. Continuous and dashed lines correspond to patients with cetuximab global clearance below and above the median value, respectively.

saturable elimination of this 2-compartment model was described by a zero-order constant k_0 .¹⁷ Similarly to the latter study, we found that cetuximab pharmacokinetics was best described using a 2-compartment model with both first-order and saturable (zero-order) elimination. The elimination of plasma proteins, including IgG and albumin, occurs through intracellular catabolism, following fluid-phase endocytosis,

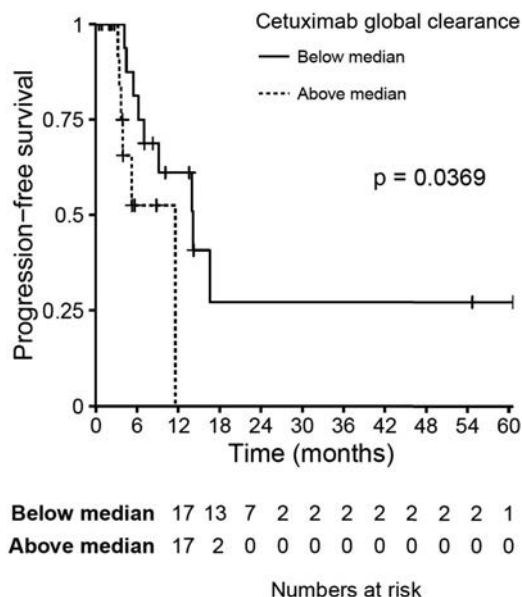


FIGURE 1. Kaplan–Meier curves of PFS according to cetuximab global clearance in all patients. Continuous and dashed lines correspond to patients with cetuximab global clearance below and above the median value, respectively.

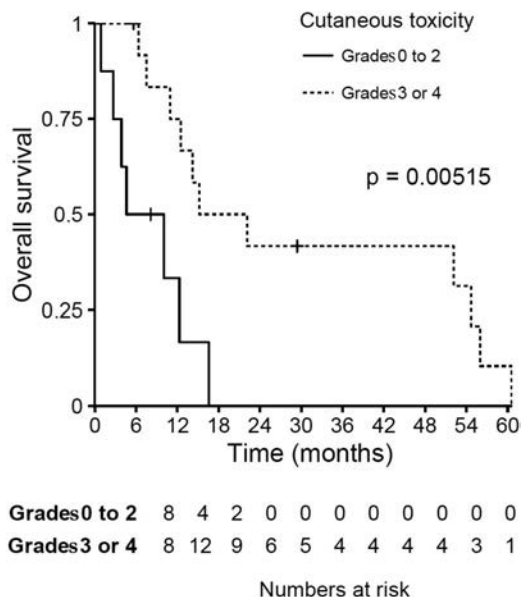


FIGURE 3. Kaplan–Meier curves of OS according to intensity of radiation dermatitis for the 21 patients with LAHNSSC; low (solid line) skin toxicities were considered from grades 0 to 2 ($n = 8$) and severe (dashed line) from grades 3 to 4 ($n = 13$).

a mechanism that is not saturable at physiological concentrations.²² Antibodies also undergo receptor-mediated elimination after binding to their target antigen. This latter elimination is, by definition, capacity-limited (saturable) because of finite availability of the target antigen. The structural model used in our cohort should therefore provide a more mechanistic description of cetuximab elimination than the other models tested because it takes into account the different mechanisms of elimination and combines nonsaturable (first-order) and saturable (zero-order) eliminations. Individual factors were previously reported to influence the pharmacokinetics of cetuximab. Tan et al reported a significant association between cetuximab clearance and both BSA and body weight.¹³ Azzopardi et al¹⁷ observed an increase in V_1 , V_2 , and k_0 with BSA and an inverse relationship between initial serum albumin concentration and the nonsaturable component of cetuximab elimination (CL). In our cohort, we observed the expected influence of BSA on V_1 and V_2 , which justifies that cetuximab dose is adjusted to BSA. We could not test the association between serum albumin concentrations and cetuximab pharmacokinetic parameters. We report for the first time an influence of associated chemotherapy on both first-order elimination clearance (CL) and the saturated elimination rate (k_0) of cetuximab. Compared with patients treated with cetuximab monotherapy, CL was lower and k_0 was higher in patients receiving chemotherapy. The parameter k_0 should quantify the saturated (specific) component of cetuximab elimination, related to its binding to EGFR. A hypothesis to explain this result on k_0 could be that patients receiving chemotherapy had more severe disease, and therefore more EGFR available for cetuximab binding. In addition, the destruction of cancer cells induced by chemotherapy may have led to an increased release of EGFR. In contrast, CL, which should quantify the first-order (nonspecific) elimination of cetuximab, was lower in patients receiving chemotherapy. Two previous studies have analyzed the relationship between cetuximab pharmacokinetics and efficacy. Fracasso et al¹³ observed higher cetuximab trough concentrations in responders than in nonresponders, in a cohort of patients treated for different types of carcinomas. The average trough level of patients with both response and stable disease was 60.7 mg/L compared with 33.2 mg/L in patients with progressing disease. Azzopardi et al¹⁷ reported a relationship between cetuximab global clearance (cumulative cetuximab dose divided by cumulative AUC) and PFS of patients with metastatic colorectal cancer. The risk of disease progression increased significantly with decreasing cetuximab global clearance. In this study, disease progression was significantly associated with cetuximab global clearance, with a longer PFS in patients with cetuximab global clearance below the median value ($P = 0.037$). OS was also significantly associated with cetuximab global clearance, with a longer OS in patients with low cetuximab global clearance ($P = 0.007$). These results are important and can be explained by the fact that patients with a higher exposure to cetuximab had longer PFS and OS.

In patients treated with anti-EGFR monoclonal antibodies for colorectal or HNSCC cancers, skin toxicity (as rash or folliculitis) was previously reported to be associated with response: patients with high-grade skin toxicities having better response or survivals, when treated with panitumumab^{23,24} or cetuximab.^{2,4,25} However, in metastatic HNSCC, Vermorken

et al³ found no significant association between severity of skin toxicity and survival ($P = 0.14$). No study reported an association between radiation dermatitis and survival data. In our 21 patients with LAHNSCC treated with radiotherapy plus cetuximab, mucositis and folliculitis (equivalent to rash) were not significantly related with OS. However, patients with LAHNSCC with severe radiation dermatitis (at least grade 3) had longer OS ($P = 0.005$). The difference between skin toxicities related to radiotherapy or cetuximab in the radiation field is not easy and classifications used in these previous clinical studies were not always described. In our 21 LAHNSCC, the distinction was made with the help of an adapted classification.^{26,27} In our cohort, the PFS and OS were not different between patients with MHNSCC and LAHNSCC ($P = 0.09$ and $P = 0.125$, respectively), probably because of relatively small groups. This may also be explained by the fact that many patients in the LAHNSCC population with curative intent relapsed precociously and, on the other side, some patients with MHNSCC had excellent survival after 1 year.

CONCLUSIONS

In conclusion, a model with combined linear and non-linear mechanisms of elimination allowed a good description of cetuximab pharmacokinetics. Exposure to cetuximab is assessed by its global clearance. The risk of disease progression and death decreased significantly with decreasing cetuximab global clearance for patients with HNSCC treated with radiotherapy or chemotherapy. These results strongly indicate that cetuximab dose and dosing regimen could be optimized in such a poor prognosis population, based on an individual assessment of pharmacokinetics, to prolong survival. These results need to be confirmed in a prospective study.

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