available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Inter-observer agreement between dermatologists and oncologists in assessing dermatological toxicities in patients with metastatic colorectal cancer treated by cetuximab-based chemotherapies: A pilot comparative study

Jacqueline Duffour [a,*], *Simon Thézenas* [b], *Olivier Dereure* [c], *Agnès Garcin* [a], *Julie Caron* [c], *Emmanuelle Samalin* [a], *Fabienne Portales* [a], *Catherine Fiess* [a], *Patrick Chalbos* [a], *Christine Gestin-Boyer* [a], *Marc Ychou* [a], *Bernard Guillot* [c]

[a] *Department of Digestive Oncology, Val d'Aurelle, Regional Cancer Centre, Montpellier Cedex 5, France*
[b] *Biostatistics Unit, Val d'Aurelle, Regional Cancer Centre, Montpellier Cedex 5, France*
[c] *Department of Dermatology, University Hospital, Montpellier, France*

ARTICLE INFO

Article history:
Received 18 December 2009
Received in revised form 2 March 2010
Accepted 12 March 2010
Available online 21 April 2010

Keywords:
Cetuximab
Colorectal cancer
Grading
Rash acne

ABSTRACT

The aim of this study was to measure the inter-observer agreement between two teams of three dermatologists and oncologists in labelling and grading the cetuximab-induced dermatological toxicities from 98 photographs performed in a cohort of 15 patients with metastatic colorectal cancer receiving cetuximab-based chemotherapy. Kappa coefficient (κ) assessed inter-observer grading agreement. Both teams defined by the same terms eight of the 13 (62%) toxic effects reported together. Discrepancies concerned the labelling of rash desquamation, hand–foot syndrome and xerosis and the grading (different and often going in the opposite direction) of various toxicities such as paronychia, xerosis, desquamation and hand–foot syndrome (κ value less than 0.40). Acneiform eruption was recognised by both teams, but the grading allocated by oncologists was lower. Our results suggested the need for a real consensus between oncologists and dermatologists for labelling and grading these dermatological toxicities. Better training of oncologists by using a dermatological atlas would improve inter-observer agreement.

1. Introduction

Globally, colorectal cancer is one of the three most commonly diagnosed malignancies.[1] Recently, new targeting therapies (including cetuximab) have been added to systemic cytotoxic chemotherapy combining irinotecan and/or oxaliplatin with fluorouracil and leucovorin in the treatment of this cancer. They provided further improvements, particularly in terms of efficacy[2–4] and secondary resection rates.[5,6] Thus, cetuximab is approved for the treatment of refractory metastatic colorectal cancer, either in combination with irinotecan[2,3] or as monotherapy[2,7] and recently when combined with FOLFIRI or FOLFOX regimens, for patients expressing KRAS wild-type metastatic colorectal cancer.[8,9] Cetuximab is a chimeric mouse–human IgG1 monoclonal antibody that binds, with high affinity and specificity, to the extracellular domain of

* *Corresponding author:* Address: CRLC Val d'Aurelle, Parc Euromédecine, 34298 Montpellier Cedex 5, France. Tel.: +33 (0)467 61 85 65; fax: +33 (0)467 61 25 72.
E-mail address: jduffour@valdorel.fnclcc.fr (J. Duffour).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2010.03.008

epidermal growth factor receptor (EGFR). It interferes with the downstream signalling cascade, leading to inhibition of cell proliferation, angiogenesis and metastasis.[10–12] At the approved dosing regimen (400 mg/m^2 initial dose and 250 mg/m^2/week subsequently or 500 mg/m^2 every 2 weeks), cetuximab is generally well tolerated. However, it has been associated with various dermatological toxicities including xerosis, nail changes, hair changes, telangiectasia and follicular acneiform eruption. This latter, also termed acne-like rash or folliculitis,[13,14] seen in up to 86% of patients,[2,7] is sometimes a limiting adverse event (5–18% of patients with grade 3) which requires intermittent breaks in treatment or dose reduction. Most of these dermatological side-effects can induce itching, pain and also cosmetic discomfort, which, added to the classical chemotherapy toxicity, may psychologically affect the patient and above all compromise compliance with therapy. Yet data from clinical studies with cetuximab showed a positive correlation between rash and response rate[2] and/or progression-free survival.[7] Therefore, these data suggested that intuitive reduction in the dose of cetuximab due to fear of toxicity would dangerously compromise efficacy in most patients. On the other hand, the underestimation of dermatological toxicity might compromise compliance of patients. Medical oncologists usually manage some cutaneous toxicities induced by 5-FU (mainly hand–foot syndrome), but compared with dermatologists, not all of them have the accuracy of dermatological terminology. These dermatological effects potentially induced by cetuximab were usually classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCI CTCAE v3.0),[15] but some limitations and shortcomings in its use have been reported.[16,17] Apparent inconsistencies in assessing these cutaneous toxicities could affect both their recording and management. Consequently, the objective of this pilot study was to evaluate, from photographs, the inter-observer agreement between dermatologists and oncologists in labelling and grading the toxicities induced by cetuximab in metastatic colorectal patients.

2. Patients and methods

2.1. Study design

This study was a pilot, observational, non-interventional, comparative study designed to measure the inter-observer agreement between two teams (oncologists and dermatologists) in assessing the coding and grading of cetuximab-induced toxicities from photographs taken in a cohort of 15 patients treated with cetuximab. These patients with metastatic colorectal cancer received cetuximab as the standard dosing regimen (an initial 2-h intravenous infusion at 400 mg/m^2 subsequently followed by a weekly 1-h infusion at 250 mg/m^2) combined either with irinotecan alone (a 90-min intravenous infusion of 180 mg/m^2) every 2 weeks (8 patients), or with a FOLFIRINOX regimen in a phase II trial (ERBIRINOX; 7 patients). Treatment modifications were indicated for severe skin toxicities. In the case of one grade $\geqslant 3$ skin toxicity, cetuximab administration had to be delayed until grade 0 was achieved. A second or third recurrence of grade $\geqslant 3$ toxicity required dose reduction to 200 and 150 mg/m^2. Cetuximab was stopped in cases of a fourth occurrence of skin toxicity of grade $\geqslant 3$. Twelve cycles were planned except in the case of progression, unacceptable toxicity or the patient's refusal to continue.

All photographs were performed by the same operator (a clinical trial associate), with the same camera (Canon, 7.5 million pixels), in identical experimental conditions, during 2005–2006. Each patient could be photographed at various cycles and several pictures could be taken at the same cycle. Blurred or poorly lightened pictures were withdrawn. Therefore, among the 250 pictures taken, the 98 lightest and clearest have been selected because they were better qualified to diversify grades and toxicity types. They were collected in a slideshow of 44 slides of 98 pictures (one slide collecting all the pictures representing toxicities at one cycle, in 1 patient). The slides were randomly allocated to two experienced teams, one made up of three oncologists from the Regional Cancer Centre, the other one of three dermatologists from the University Hospital.

For each slide, one or various dermatological toxicities were to be defined and graded according to the CTCAE 2006, v3.[15]

Thus, some terms such as rash acne/acneiform, cheilitis, ulceration, nail changes, dry skin, hyperpigmentation, and hand–foot syndrome were included in the CTCAE, v3, but all observers could use any different dermatological terms that seemed to better define cutaneous lesions: paronychia, eyelid dysfunction, desquamation, scabs, etc.

The time allocated to each team to view one slide was identical. Secondarily, a consensus collegial assessment was collected by slide and by team. To avoid potential bias, no details of patient history except dermatological symptoms (such as pain, itching or percentage of body surface area covered by lesions), were available. Each patient provided oral consent to be photographed and confidentiality was respected.

2.2. Statistical analysis

Qualitative data (expressed by percentages) were compared using Chi-squared test or Fisher's test (when applicable). Quantitative data were expressed by median and range. The inter-observer grading agreement was assessed by kappa coefficient. Guidelines for the interpretation of kappa (κ) were: $\kappa < 0.40$, poor agreement; $\kappa = 0.41$–0.75, moderate agreement; $\kappa > 0.75$, good agreement. Statistical analysis was performed with STATA 9.0 software. A two-sided p value of less than 0.05 was considered to indicate statistical significance.

3. Results

The patients' characteristics are presented in Table 1.

Agreement results were based on the comparative assessment of both teams according to the toxicities themselves (inter-observer agreement for the number and the type of toxic effects) and their grading.

On the whole, among the 29 terms proposed by the CTCAE 2006, v3, the two teams used 13 terms all together to define dermatological toxic effects. Eight of them (61.8%) were common to both teams to define one lesion. Oncologists and

Table 1 – Patient characteristics.

Characteristics	Patients	
	No.	%
All patients	15	
Tumour site		
Colon	8	53.3
Rectum	7	46.7
Number of previous treatment lines		
0	7	46.7
⩾1	8	53.3
Age		
Median		65
Range		38–79
Number of pictures/slide		
Median		2
Range		1–4
Number of slides/patient		
Median		2
Range		1–9

dermatologists agreed with terms frequently used such as acneiform rash (22 times versus 23), paronychia (12 times versus 10) and cheilitis (5 times versus 4), but disagreed with others such as xerosis (1 time versus 10), hand–foot syndrome (8 times versus 2) and rash desquamation (12 times versus 7), respectively. Other unusual toxicities, such as ulcerations and dry eyes, seemed consensual, but they were identified less than twice by one or the other team and they did not result in agreement. Five toxicity terms (38.5%) were differently used by the observers to define the same lesion. Nail changes and eyelid dysfunction were never proposed as toxicities by the oncologists, and scab and hyperpigmentation were never used by dermatologists. Finally, some cutaneous lesions defined as hand–foot syndrome by oncologists were labelled xerosis by dermatologists (four times of nine; Figs. 1 and 2).

Grading assessment has been reported per slide and per toxicity in the case of frequently observed effects. Table 2 reports the association between observer teams and maximum grading of all the toxic effects observed per slide. Oncologists and dermatologists disagreed only with the grading 3–4 of rash, which was lower among oncologists than among dermatologists (4/44 slides (9.1%) versus 11/44 (25%), $p = 0.047$). When agreement between observers for various toxicities was assessed with the kappa coefficient, inter-observer consensus in various frequently observed dermatological effects was even less evident. The κ value between the two teams, assessing their grading for the five toxicities more frequently observed (paronychia, rash acne, xerosis, desquamation and hand–foot syndrome) was less than 0.40 and demonstrated a limited inter-observer agreement (Table 3). Maximum grading noted by both observers for all the slides affected by these toxicities is detailed in Table 4. For most of these toxicities (particularly paronychia and desquamation), grading of the same lesion was not only different, but was going in the opposite direction as well. As for acneiform rash, the observers disagreed on the grading, but both moved towards the same

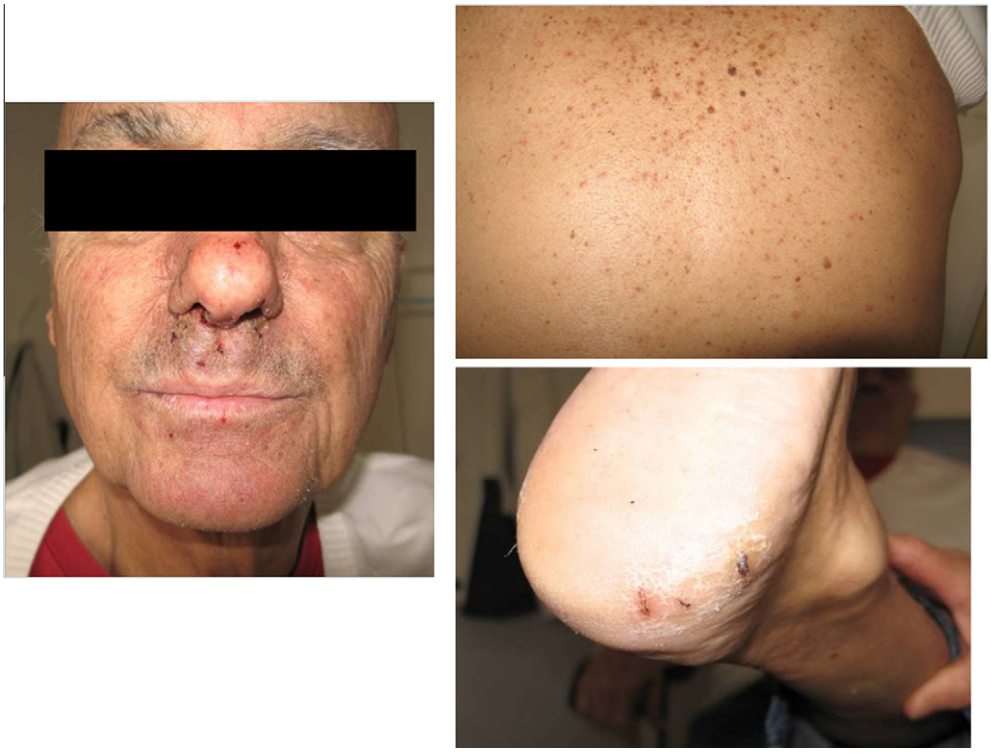

Fig. 1 – Discrepancies between oncologists and dermatologists regarding the assessment of skin lesions induced by cetuximab in patient X. Oncologists: grade 2 rash and grade 2 hand–foot syndrome. Dermatologists: grade 2 xerosis.

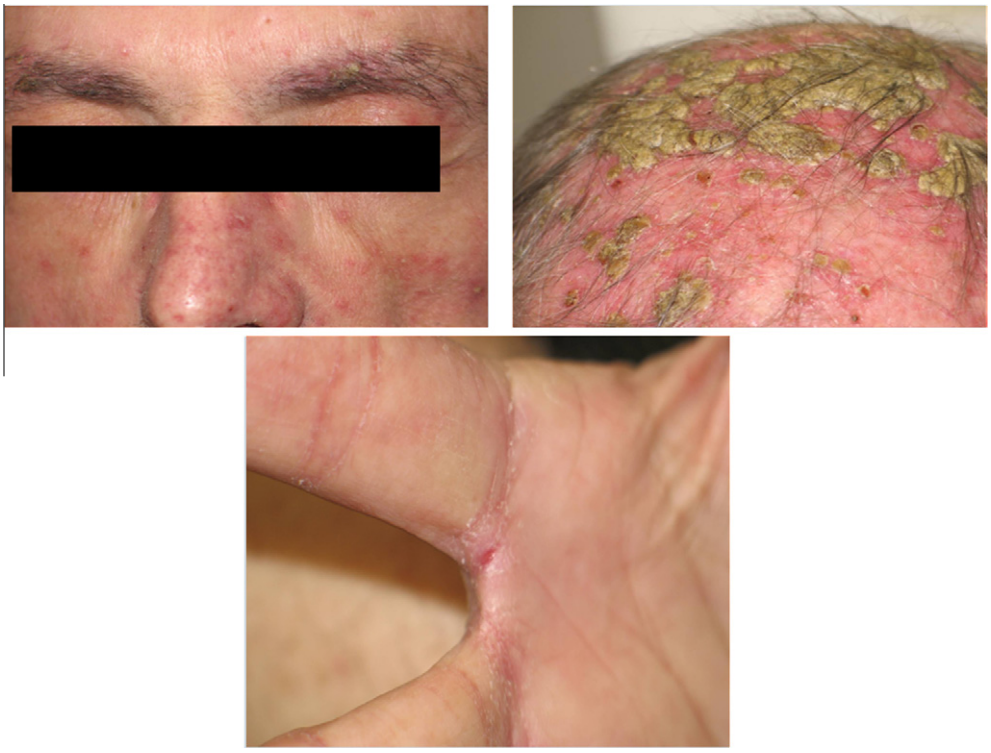

Fig. 2 – Discrepancies between oncologists and dermatologists regarding the assessment of skin lesions induced by cetuximab in patient Y. Oncologists: grade 2 acne, grade 3 scabs and grade 1 hand–foot syndrome. Dermatologists: grade 3 rash acneiform, grade 2 ulceration and grade 2 rash desquamation.

grade of severity, and compared with oncologists, dermatologists systematically allocated a higher grade to all the slides relating to this toxicity.

4. Discussion

This is the first study to measure the consensus between two specialist groups, oncologists and dermatologists, regarding the assessment of dermatological toxicities induced by cetuximab, depending on definitions, the number of lesions observed and their grading. Even if most of the toxic effects (about 62%) were defined by the same terms by both teams, there were significant discrepancies regarding the labelling of a few (xerosis, hand–foot syndrome and rash desquamation). Disagreement was complete with regard to 'hand–foot syndrome', so-called by oncologists and labelled as xerosis by dermatologists. Both teams

Table 2 – Toxicity (maximum grade per slide) reported by oncologists and dermatologists (44 slides).

	Oncologists					Dermatologists					
	Grade 0 No. (%)	Grade 1 No. (%)	Grade 2 No. (%)	Grade 3 No. (%)	Grade 4 No. (%)	Grade 0 No. (%)	Grade 1 No. (%)	Grade 2 No. (%)	Grade 3 No. (%)	Grade 4 No. (%)	*p* (Gr 3/4)
Chelitis	39 (88.6)	2 (4.5)	2 (4.5)	1 (2.3)	0 (0)	40 (90.9)	3 (6.8)	1 (2.3)	0 (0)	0 (0)	NS
Xerosis	43 (97.7)	1 (2.3)	0 (0)	0 (0)	0 (0)	34 (77.3)	5 (11.4)	5 (11.4)	0 (0)	0 (0)	NS
Hyperpigmentation	43 (97.7)	1 (2.3)	0 (0)	0 (0)	0 (0)	44 (100)	0 (0)	0 (0)	0 (0)	0 (0)	NS
Nail changes	44 (100)	0 (0)	0 (0)	0 (0)	0 (0)	42 (95.5)	2 (4.5)	0 (0)	0 (0)	0 (0)	NS
Pruritus	43 (97.7)	1 (2.3)	0 (0)	0 (0)	0 (0)	44 (100)	0 (0)	0 (0)	0 (0)	0 (0)	NS
Desquamation	32 (72.7)	9 (20.5)	2 (4.5)	1 (2.3)	0 (0)	37 (84.1)	5 (11.4)	2 (4.5)	0 (0)	0 (0)	NS
Acne	22 (50)	9 (20.5)	9 (20.5)	4 (9.1)	0 (0)	21 (47.7)	4 (9.1)	8 (18.2)	11 (25)	0 (0)	0.047
HFS[a]	36 (81.8)	4 (9.1)	4 (9.1)	0 (0)	0 (0)	42 (95.5)	1 (2.3)	1 (2.3)	0 (0)	0 (0)	NS
Ulceration	43 (97.7)	0 (0)	0 (0)	1 (2.3)	0 (0)	43 (97.7)	0 (0)	1 (2.3)	0 (0)	0 (0)	NS
Paronychia	32 (72.7)	3 (6.8)	5 (11.4)	4 (9.1)	0 (0)	34 (77.3)	0 (0)	8 (18.2)	2 (4.5)	0 (0)	NS
Dry eyes	43 (97.7)	0 (0)	0 (0)	1 (2.3)	0 (0)	42 (95.5)	0 (0)	1 (2.3)	1 (2.3)	0 (0)	NS
Eyelid dysfunction	44 (100)	0 (0)	0 (0)	0 (0)	0 (0)	42 (95.5)	1 (2.3)	0 (0)	1 (2.3)	0 (0)	NS
Scabs	42 (95.5)	0 (0)	1 (2.3)	1 (2.3)	0 (0)	44 (100)	0 (0)	0 (0)	0 (0)	0 (0)	NS

[a] HFS: hand–foot syndrome.

Table 3 – κ values of agreement between oncologists and dermatologists when assessing the grading of five main toxicities.

	Agreement (%)	κ
Paronychia	70.4	0.34
Acneiform rash	36	0.142**
Xerosis	10	0.05**
Desquamation	62	–0.31**
HFS[a]	0	–0.23**
Chelitis		

$\kappa < 0.40$ or $\kappa < 0$, poor agreement; $\kappa = 0.41$–0.75, moderate agreement; $\kappa > 0.75$, good agreement.

[a] HFS: hand–foot syndrome.

** Significant.

disagreed with the grading of some important toxicities frequently observed, such as paronychia, rash acne, xerosis, desquamation and hand–foot syndrome (κ value less than 0.40). As for follicular acneiform eruptions, which are the most frequently reported adverse effects of cetuximab, they were recognised by both teams, but apparently, compared with dermatologists, oncologists took them less seriously. This study emphasised that it was difficult for oncologists, insufficiently trained in this speciality, to label various dermatological toxicities well, and for dermatologists to use the NCI CTCAE 2006, v3, considered too simplified and inappropriate. As an example, paronychia, a common toxicity induced by cetuximab, was not included in this version of the grading system. The new toxicity grading system (CTCAE-2009-v4), had significant improvements. Compared with the version 3.0, the dermatological part was much more detailed and included 34 adverse events compared with 27. All the cutaneous disorders were defined and characterised. Some of them, such as nail changes, have been developed (three categories of nail disorders now compared with one, but none including paronychia). Rash acne, also termed acne-like rash or folliculitis, was too vague and defined both early pustular facial acneiform eruptions, and late eczematous lesions associated with distal xerosis and sometimes pruritus. Unlike version 3.0, NCI CTCAE version 4.0 based the severity of several adverse events on body surface area coverage, including skin rash. Now, this later skin lesion is generally confined to the face and upper trunk, whatever the severity. Finally, neither of the two versions considered quality of life or discomfort of the patients and were not fully satisfactory. Given the specific nature of dermatological toxicities induced by cetuximab, various authors had already pre-empted classification adjustments. Lynch et al.[17] proposed a simpler and more appropriate grading system divided into three classes (mild, moderate and severe toxicity). Pérez-Soler et al.[18] proposed to subdivide patients with grade 2 rash based on its tolerability (grade 2A, tolerable; grade 2B, interfering with daily life and needing intervention or management; grade 3, being really dose limiting). Indeed, effective treatment of EGFR inhibitor-associated dermatological effects depends to a large extent on accurate grading, allowing an adequate therapeutic strategy. Until then, treatment will continue to be inspired by non-standardised practical guidelines based mainly on personal experience.[19–22] Three recent trials assessing primary pre-emptive strategies for these specific skin toxicities showed some efficacy of minocycline,[23] tetracycline[24] and doxicycline.[25] Overall, management as a comparison of these preventive or curative treatments requires non-ambiguous labelling and grading systems. Our data showed precisely how an agreement was difficult to reach in practice. There are, however, some limitations to our study. The photographs, although presented in any order, had not previously been randomized since being selected by an observer depending on the degree of sharpness. In order to speed up calculations, intra-observer agreement was assessed verbally and not calculated via the κ coefficient. Given the highly specific clinical and dermatological references of each team, we might suppose that oncologists and dermatologists had consensual responses. Assessing these intra-observer agreements could be the purpose of a future study. We studied a relatively small number of patients. Nevertheless, the number of pictures was large enough to demonstrate significant discrepancies between teams in defining or grading toxicities. This study demonstrated the need for a real consensus between oncologists and dermatologists both for labelling and grading the various dermatological toxicities potentially induced by cetuximab. It is important, within a possible collaboration, to better train the oncologists, perhaps using an atlas of dermatology. What is the interest of such an agreement since mainly oncologists used to manage these toxicities? Actually, it is very important for such different specialised medical fields to use the same common vocabulary and above all, grade in the same way, in order to better manage these toxicities in clinical research and therapeutic recommendations.

Hence, a new agreement study of the two teams could be performed, but after the oncologists had benefited from effective dermatological support.

Table 4 – Grading of most frequent toxicities observed by oncologists and dermatologists (all slides concerned).

	Paronychia (12 slides)	Rash acne (25 slides)	Desquamation (15 slides)	Xerosis (10 slides)	HFS* (9 slides)
Slides with same grading between oncologists and dermatologists	6/12	9/25	4/15	1/10	0
Slides with lower grading from oncologists	3/12	14/25	3/15	9/10	1/9
Slides with higher grading from oncologists	3/12	2/25	8/15	0	8/9

* HFS: hand–foot syndrome.

Conflict of interest statement

None declared.

Acknowledgements

There is no funding source for this study. The authors are indebted to Dr. Karim Tifratène and Joelle Mazel (Merck, Serono, France) who facilitated the execution of the study.

REFERENCES

1. Ferlay J, Autier P, Boniol M, et al. Estimates of the cancer incidence and mortality in Europe in 2006. *Ann Oncol* 2007;**18**:581–92.
2. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004;**351**:337–45.
3. Wilke H, Glynne-Jones R, Thaler J, et al. Cetuximab plus irinotecan in heavily pretreated metastatic colorectal cancer progressing on irinotecan: MABEL study. *J Clin Oncol* 2008;**26**:5335–43.
4. Lenz HJ, Van Cutsem E, Khambata-Ford S, et al. Multicenter phase II and translational study of cetuximab in metastatic colorectal carcinoma refractory to irinotecan, oxaliplatin, and fluoropyrimidines. *J Clin Oncol* 2006;**24**:4914–21.
5. Adam R, Aloia T, Levi F, et al. Hepatic resection after rescue cetuximab treatment for colorectal liver metastases previously refractory to conventional systemic therapy. *J Clin Oncol* 2007;**25**:4593–602.
6. Gruenberger B, Tamandl D, Schueller J, et al. Bevacizumab, capecitabine, and oxaliplatin as neoadjuvant therapy for patients with potentially curable metastatic colorectal cancer. *J Clin Oncol* 2008;**26**:1830–5.
7. Saltz LB, Meropol NJ, Loehrer Sr PJ, et al. Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. *J Clin Oncol* 2004;**22**:1201–8.
8. Van Cutsem E, Kohne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009;**360**:1408–17.
9. Bokemeyer C, Bondarenko I, Makhson A, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2009;**27**:663–71.
10. Mandal M, Adam L, Mendelsohn J, Kumar R. Nuclear targeting of Bax during apoptosis in human colorectal cancer cells. *Oncogene* 1998;**17**:999–1007.
11. Perrotte P, Matsumoto T, Inoue K, et al. Anti-epidermal growth factor receptor antibody C225 inhibits angiogenesis in human transitional cell carcinoma growing orthotopically in nude mice. *Clin Cancer Res* 1999;**5**:257–65.
12. Prewett MC, Hooper AT, Bassi R, et al. Enhanced antitumor activity of anti-epidermal growth factor receptor monoclonal antibody IMC-C225 in combination with irinotecan (CPT-11) against human colorectal tumor xenografts. *Clin Cancer Res* 2002;**8**:994–1003.
13. Jacot W, Bessis D, Jorda E, et al. Acneiform eruption induced by epidermal growth factor receptor inhibitors in patients with solid tumours. *Br J Dermatol* 2004;**151**:238–41.
14. Guillot B, Bessis D. Clinical appearance and management of cutaneous side effects of EGF receptor inhibitors. *Ann Dermatol Venereol* 2006;**133**:1017–20.
15. National Cancer Institute. Common terminology criteria for adverse events v.3.0; 2006. <http://ctep.cancer.gov/reporting/ctc.html>.
16. Hidalgo M, Siu LL, Nemunaitis J, et al. Phase I and pharmacologic study of OSI-774, an epidermal growth factor receptor tyrosine kinase inhibitor, in patients with advanced solid malignancies. *J Clin Oncol* 2001;**19**:3267–79.
17. Lynch Jr TJ, Kim ES, Eaby B, et al. Epidermal growth factor receptor inhibitor-associated cutaneous toxicities: an evolving paradigm in clinical management. *Oncologist* 2007;**12**:610–21.
18. Pérez-Soler R, Delord JP, Halpern A, et al. HER1/EGFR inhibitor-associated rash: future directions for management and investigation outcomes from the HER1/EGFR inhibitor rash management forum. *Oncologist* 2005;**10**:345–56.
19. Shah NT, Kris MG, Pao W, et al. Practical management of patients with non-small-cell lung cancer treated with gefitinib. *J Clin Oncol* 2005;**23**:165–74.
20. Purdom M. Management of acneiform rashes related to gefitinib therapy. *Clin J Oncol Nurs* 2004;**8**:316–7.
21. Herbst RS, LoRusso PM, Purdom M, Ward D. Dermatologic side effects associated with gefitinib therapy: clinical experience and management. *Clin Lung Cancer* 2003;**4**:366–9.
22. Segaert S, Van Cutsem E. Clinical signs, pathophysiology and management of skin toxicity during therapy with epidermal growth factor receptor inhibitors. *Ann Oncol* 2005;**16**:1425–33.
23. Scope A, Agero AL, Dusza SW, et al. Randomized double-blind trial of prophylactic oral minocycline and topical tazarotene for cetuximab-associated acne-like eruption. *J Clin Oncol* 2007;**25**:5390–6.
24. Jatoi A, Rowland K, Sloan JA, et al. Tetracycline to prevent epidermal growth factor receptor inhibitor-induced skin rashes: results of a placebo-controlled trial from the North Central Cancer Treatment Group (N03CB). *Cancer* 2008;**113**:847–53.
25. Lacouture ME, Mitchell EP, Piperdi B, et al. Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II, open-label, randomized trial evaluating the impact of a pre-emptive skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. *J Clin Oncol* 2010;**28**:1351–7.