

When treatment gets under your skin...

Caring for patients with drug-induced acneiform eruptions

→ Anna Wagstaff

EGFR inhibitors represent a bright hope for modern cancer therapies. But treatment comes at a price – an acne-like rash and other skin problems that can blight people's lives. As these drugs become used more widely and at earlier stages of treatment, it becomes increasingly urgent to learn how to treat the side-effects and help patients.

“IT was an odd feeling in the skin. You have seen those horror movies. My skin was popping up, and pimples were breaking out. They were quite big and a little bit itchy. It's like acne for young people. It was blistering up in my face and my hair.”

This is how one patient describes the feeling when, six days into his first course of cetuximab (Erbix), he started to develop the acne-like skin rash that is one of the known side-effects of drugs of that class. For the next month, Jan Andersen opted to stay out of the public eye as far as possible, and went to work in the evenings when the office was empty. “I could have shown myself, but I didn't want to, because I would have scared people and I'd have been asked so many questions.”

With the passage of time and some helpful advice, the rash has set-

tled down. Today, Andersen's regular dose of cetuximab leaves him with some red spots around the base of the nose and on the chin. His colleagues have got used to the sight of his face, and he is not too bothered about the problem. “I still have some on my body, but those pimples are drying up and falling off and it is not bad any more. I can handle it.” More of an issue is the inflammation around his fingernails and toenails, which developed around a month into the treatment, and is another characteristic side-effect of the drug, along with dry skin, skin fissures, and problems around the eyes, nose and, in women, the vagina.

Cetuximab is one of a growing class of drugs aimed at inhibiting the receptors for epidermal growth factor (EGF), which plays a major role in the development of many solid tumours and is associated with aggressive disease, increased resistance to chemotherapy and radiotherapy, increased metastasis, poor clinical

prognosis and decreased survival.

The skin problems that Andersen continues to experience appear to be common to all drugs that inhibit EGFR function. This is true of monoclonal antibodies such as cetuximab, panitumumab (approved in the US but not yet in Europe) or matuzumab (still in phase II trials), all of which block the EGF receptor on the outside of cell. It is also true of small molecules such as erlotinib (Tarceva) and gefitinib (Iressa), which block the tyrosine kinase pathways that send the erroneous signal from the receptor, to the inside of the cell, and of drugs using other mechanisms of action such as recombinant EGF vaccines or anti-sense technologies.

Current knowledge strongly indicates that the mechanism causing the skin problems is the same as the mechanism that suppresses the tumour, which means that you cannot inhibit EGFR without affecting the normal functioning of the skin. As EGFR inhibitors look set to play an expanding role, with



women. They don't like to have pimples because they are afraid of the reaction of other people, who may say 'you are not taking care of yourself,' and so on. Some of these patients do not want to go out any more."

Segaert emphasises that skin rashes can be effectively controlled with the right treatment and time. This treatment is not just cosmetic. Segaert has seen patients come off the drug because they couldn't live with what it did to their face. "There are some who say: I would rather die than walk around with pimples. This is something oncologists found very hard to understand at first. Of course we [dermatologists] are used to people with skin disease so we do not underestimate the problem, but I think oncologists were surprised by the strong reaction of patients."

a variety of drugs used in a variety of solid tumours, including early disease, skin problems will become increasingly prevalent. Clinicians, nursing staff, patients and carers need to be equipped to deal with them.

Dermatologist Siegfried Segaert has worked with patients like Jan Andersen since 2003, when Eric Van Cutsem of the Digestive Oncology Unit of the Gasthuisberg University Hospital in Leuven, Belgium, started entering patients with metastatic colorectal cancer into clinical trials.

Segaert says it took some oncologists a while to understand the extent to which these skin problems affect patients' quality of life. "Almost 80% of patients have these side effects to some degree. In the beginning people thought, this is not dangerous for health, not life-threatening, it is not like the severe nausea, vomiting, hair loss, diarrhoea you get with classic anti-cancer drugs. It's just a few pimples.

"The problem with this eruption is that you cannot hide it. It has a large impact on self-esteem, especially with

HOW BAD CAN IT GET?

The acneiform eruption (acne-like rash) is one of a series of skin problems associated with EGFR inhibitors, though it is probably the one most patients find hardest to cope with. It tends to appear relatively quickly, three days to three weeks after starting on the drug, peak in severity early on, then settle down in a matter of weeks. However, it is likely to remain present at some level.

This eruption tends to be concentrated on the face, neck, scalp and upper torso. The pimples are often itchy

GRADING OF ACNEIFORM ERUPTION			
GRADE 1	GRADE 2	GRADE 3	GRADE 4
Rash/desquamation			
Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus [itchiness] or other associated symptoms; localized desquamation or other lesions covering <50% of body	Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering ≥50% of body	Generalized exfoliative, ulcerative, or bullous dermatitis
Rash: acne/acneiform			
Intervention not indicated	Intervention indicated	Associated with pain, disfigurement or desquamation	

National Cancer Institute Common Toxicity Criteria v3.0

and fill with pus, usually drying out to form a yellow crust. The face may also be covered in irritated red patches with inflamed capillaries, though these usually disappear after a while.

This acneiform eruption ranges from asymptomatic skin lesions, to a rash with severe itching or pain through to acute extensive skin toxicity requiring the sort of specialist treatment given at a burns unit. The rash has been classified into four grades of severity according to the National Cancer Institute Common Toxicity Criteria (NCI CTC v3.0, see above).

Around 70%–90% of patients on EGFR-inhibiting monoclonal antibodies are likely to develop some level of rash, while 5%–18% develop a severe rash. Grade 3/4 rash appears much less common with the tyrosine kinase inhibitors gefitinib and erlotinib (see box, below, right), but this may be due to the fact that doses are limited by other side-effects such as diarrhoea.

Around eight weeks after starting on one of these drugs, up to 35% of patients develop very dry, scaly and itchy skin on the arms and legs as well as the areas previously affected by the acneiform eruption. This complicates the management of the problem, as the treatments that are good for dry skin can exacerbate the rash, and vice-

versa. Dry skin may be particularly bad at the tips of the fingers and toes, and can crack, resulting in painful fissures at the knuckles and around the nails. As the skin becomes more fragile, the condition can become complicated with infection by *S. aureus* or even herpes simplex virus.

Later still, around 14 weeks after the start of therapy, about 10% of patients develop swelling and inflammation around the nails (paronychia) resembling in-growing toenails. This does not usually fade over time, and can make it very painful to walk, or even to hold a book or a newspaper. It is very difficult to cure, but the symptoms can be alleviated. Patients may also develop ulcers in the nose or mouth, vaginal dryness and problems around the eyes.

None of these symptoms were previously unknown, but Segaert says that

the whole picture, combining so many different skin problems in one patient, is unique. “I had never seen anything like this before. It was like a new skin disease caused by this targeted therapy.”

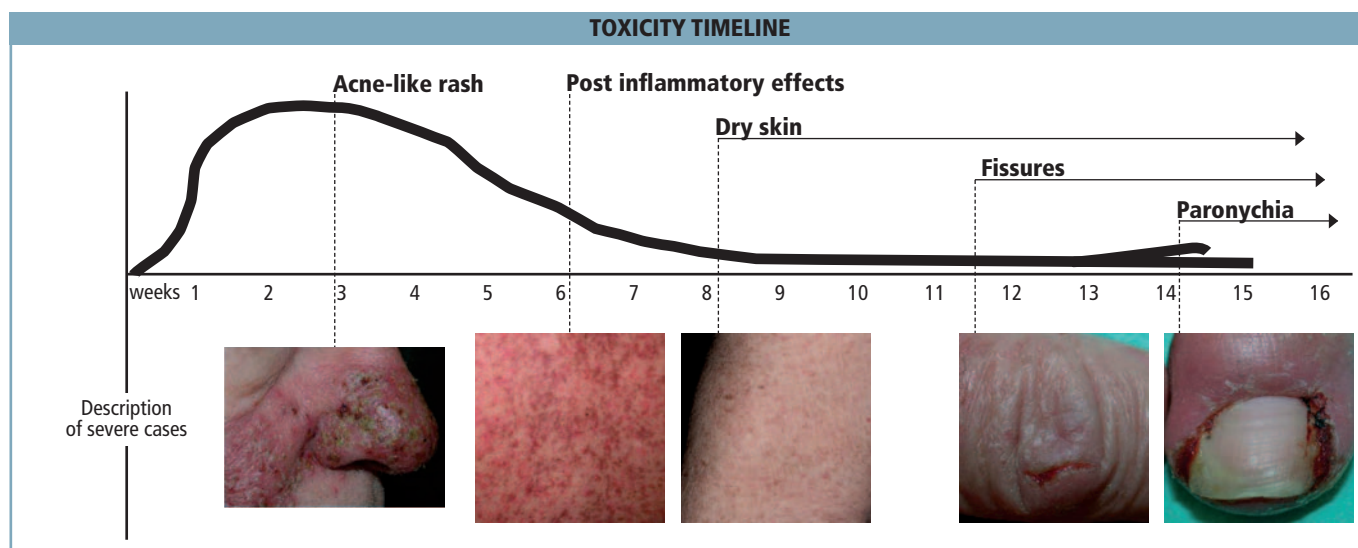
It is clearly important for health professionals and patients to learn how best to manage these distressing skin problems. There are also two additional reasons that make this an urgent issue.

The first is that almost all the evidence now indicates that people who experience a more severe skin reaction benefit most from the drug treatment. A consistent picture is emerging of a close correlation between skin rash and response for a number of EGFR inhibitors in a variety of tumours (see p 18). (This is not universal: some patients with little or no skin rash may respond, while some patients may have the rash without a strong response.) Furthermore, both skin rash and response appear to vary according to the dose. This means that far from hoping to avoid these skin problems, in the future, patients with a mild or no rash may be encouraged to increase the drug dose to the point that a grade 2 or greater rash develops.

This is a possibility being investigated in the EVEREST trial, led by Van Cutsem. Patients being treated for metastatic colorectal cancer who show little skin rash (grade 1 or less) are randomised to stay on the standard weekly dose of 250 g/m²/w cetuximab + irinote-

INCIDENCE OF ACNEIFORM ERUPTION		
EGFR INHIBITOR	PATIENTS WITH SOME RASH	PATIENTS WITH SEVERE RASH
Cetuximab	80%–86%	5.2%–18% patients ≥ grade 3. Rash tends to be more severe when given in combination with irinotecan
Panitumumab (1–2.5 mg/kg/week)	70%–100%	±10% severe
Panitumumab (6 mg/kg/week)	90%	16% ≥ grade 3
Erlotinib (150 mg/day)	67%–79%	2.6%–10.4% ≥ grade 3
Gefitinib (50–700 mg/day)	53% (0%–78%)	1.6% ≥ grade 3
Gefitinib (150–1000 mg/day)	65%	2.2% grade 3
Lapatinib (+capecitabine)	26%	2% grade 3

Sources include: S Segaert, E Van Cutsem. Clinical signs, pathophysiology and management of skin toxicity during therapy with epidermal growth factor receptor inhibitors. *Ann Oncol*, vol 16, p 1426 © European Society for Medical Oncology



EGFR inhibitors are associated with a unique combination of skin side-effects, which complicates treatment options. The acne-like rash tends to flare up quickly, and usually settles down after a few weeks; dry skin, fissures and nail problems may kick in after two or three months

Source: TARGET, European Oncology Nursing Society; pictures courtesy of Siegfried Segært

can or to have their dose progressively increased in steps of 50 g/m²/w up to a maximum of 500 g/m²/w until a rash of at least grade 2 severity appears or a tumour response occurs.

Early results (24 weeks), which were reported at the gastrointestinal meeting of the American Society of Clinical Oncology (ASCO GI) in Orlando in January, show a partial response rate of 30% in the dose-escalation arm compared to 13% in the control arm, although the control arm shows a higher proportion of patients with stable disease (56% vs 43%) and a slightly lower proportion with disease progression (22% vs 27%). Van Cutsem believes these results are very encouraging, but stresses it is early days yet, and clinicians should not increase the dose beyond the current recommended levels outside of a clinical trial.

The second reason why it is becoming more urgent to spread knowledge and experience about managing skin problems is that EGFR inhibitors are

set to be used for an increasing variety of cancers, and are coming into use at an increasingly early stage.

Clinical trials are investigating the use of EGFR inhibitors as a second- or even first-line treatment for metastatic colorectal cancer. Other trials, such as PETACC 8 (Pan-European Trials in Alimentary Tract Cancer), are looking at the effectiveness of cetuximab given in combination with an oxaliplatin-based chemotherapy as an adjuvant therapy in patients with fully resected grade III colon cancers. There are already signs that patients receiving the drug in these earlier settings are finding it harder to accept the skin side-effects.

This is perhaps not surprising. For the first generation of patients like Jan Andersen, EGFR inhibitors represent a chance of extra months (or more) of life. Patients receiving EGFR inhibitors in an adjuvant setting, by contrast, have no clinical evidence of disease and may never develop a recurrence or metastasis.

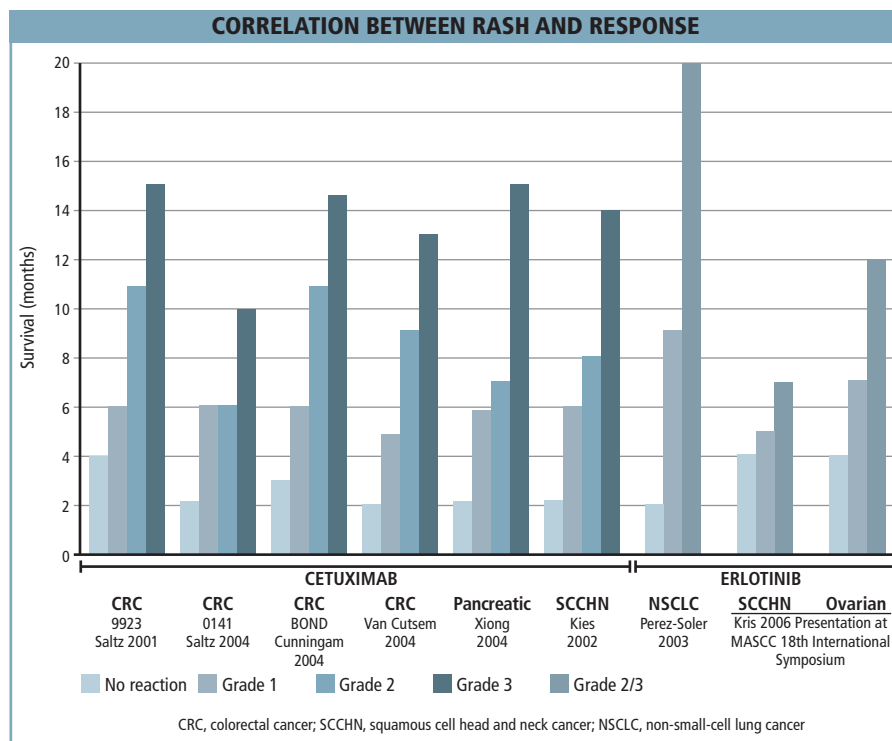
On top of this, adjuvant patients are simply less used to having cancer

and to putting up with the side-effects of cancer drugs.

Liesbeth Lemmens is a specialist nurse at the Gasthuisberg University Hospital in Leuven with several years' experience caring for colorectal patients receiving EGFR inhibitors, in settings ranging from third- or fourth-line therapies to adjuvant treatment. She sees a big difference in attitude between groups of patients. Patients treated in a third- or fourth-line setting may be more likely to say: "As long as we can live, we will accept this skin toxicity, or any toxicity at all." Patients treated in an adjuvant setting can find the side-effects harder to accept.

"They have just had their cancer diagnosis, and they need time to get used to that. They are active. They have their life and their hobbies; many of them go to work."

Jan Andersen, in contrast, had already been through four years of treatment, with at least as many different regimens before he was introduced to cetuximab, and he remembers the side-effects of all of them. "The worst



Studies looking at different EGFR inhibitors in different cancers and settings indicate a strong and consistent correlation between skin rash and clinical benefit

one was Xeloda [capecitabine]. The skin was peeling off my sole; I couldn't walk for three to four days in some cases. Then I was on oxaliplatin. I lost my hair, but that didn't matter. I could also feel a tingling in my fingers and throat when I went out into the cold. I felt a little bit tired too. Then came CPT11 [irinotecan], which had few side-effects, just a little tiredness." So when, after switching to cetuximab, his face rash confined him to his home for a month, he was philosophical about it.

Partly, it is also a matter of personality. "We had one patient who was very severely affected, who quipped: 'Well at least I can have free access to the Hallowe'en party,'" says Lemmens. "We also have patients who have only one pimple and are very upset." She points out that this is not a question of vanity. The face is fundamental to a person's sense of identity and self-

image and alters the way one is perceived by others. This can cause practical as well as personal problems. Lemmens cites the example of a patient who worked as a waiter. "He feels very well, he has a good quality of life, but he cannot go to work because nobody wants their spaghetti served by a waiter with severe skin toxicity."

"WE CAN TREAT IT"

While it is important to understand that EGFR-related skin toxicity can damage a patient's quality of life, those with experience caring for these patients believe there is another equally important message: "We can treat it."

Though there are not yet any evidence-based guidelines, and the literature on managing EGFR skin problems is still in its infancy, a number of treatment centres have developed their own protocols and are beginning to share

experiences. A conference involving oncologists and dermatologists from centres in Belgium, France, Germany, Italy, Spain and the UK has generated probably the most authoritative, experience-based, consensus guidelines to date (JDDG 2005, vol 3 pp 599–606).

Cancer nurses such as Lemmens have also been able to share their experiences and pass their knowledge on to others through the TARGET training course on molecular targeted therapies organised by the European Oncology Nursing Society.

One of the keys to managing the level of skin problems for most patients lies in good general advice – the 'Dos and Don'ts' designed to alleviate the problems on the one hand and to avoid exacerbating them on the other (see opposite). Patients need this advice in writing and a chance to discuss it both before treatment begins, to ensure they understand the principles, and during treatment, so they can adapt it according to what works best for their lifestyle.

For medical treatment of a less severe rash, the consensus recommendations published in the JDDG recommend metronidazole gel or cream, erythromycin or clindamycin gel or lotion, benzoyl peroxide gel or cream on the face or salicylic acid in alcoholic lotion on the chest/back. To get the best balance between treating the rash and treating the dry skin, which kicks in a little later, they recommend cream in preference to lotions or gels as the eruption recedes or progresses to a scaly form.

For more symptomatic rash (grade 2), oral antihistamine and/or menthol cream can be used against itchiness. Oral tetracyclines help control the inflammation. In the case of grade 3 rashes (symptomatic lesions over more than 50% of the body), the recommendation is to delay further drug

“There is a need for more research and clinical studies to develop evidence-based guidelines”

treatment. Applying saline compresses to the most inflamed areas has been found to be very effective, but also dries the skin; oral antihistamines are good for alleviating itchiness. High-dose systemic tetracyclines are recommended; however, they can sometimes be hard on the stomach, and may compound problems caused by the anti-cancer drugs. In very severe cases, where the skin is ulcerating, treatment similar to that provided in a burns unit is recommended and the patient should come off the drug.

The JDDG document also addresses management of non-rash symptoms. For dry, scaly skin, moisturising emollients are recommended. Should this develop into eczema, topical low-dose corticosteroids can be used for up to two weeks. Fusidic acid or systemic antibiotics are suggested for secondary bacterial infection or systemic antiviral drugs for viral (herpes simplex) infection. For skin fissures, early use of salicylic acid is recommended, with hydrocolloid tape or glue to help alleviate the pain.

For the inflammation around the nails – which can be painful and debilitating – there are few treatment options. Partial surgery to the nail does not appear to be an answer. The use of antiseptic/antibiotic soaks or creams may ease the pain; some dermatologists recommend a paste containing an antiseptic and anti-yeast, and in severe cases a corticosteroid, to reduce inflammation and pain. Silver nitrate can be used to treat associated pyogenic granuloma (a small rounded and often ulcerated mass of

inflamed, highly vascular granulation tissue on the skin).

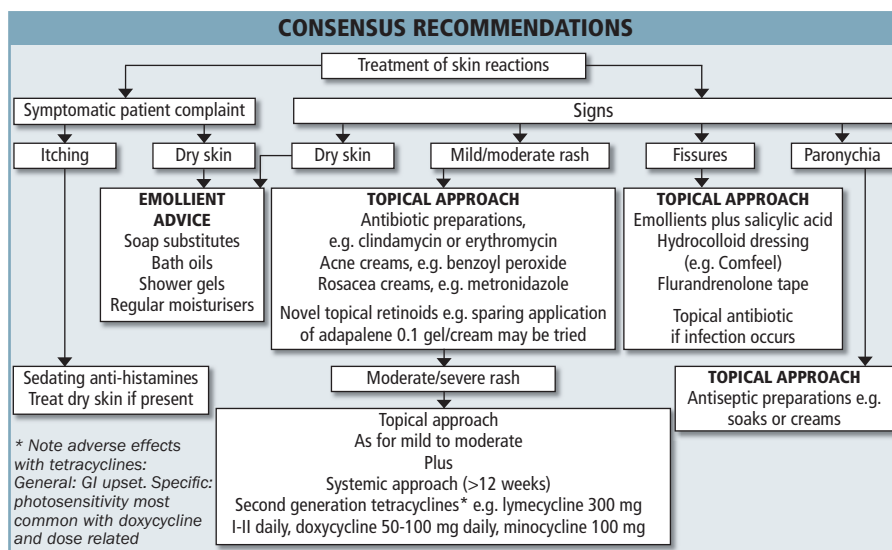
The JDDG document has to be viewed as a first stab at offering welcome guidance to professionals and patients who are grappling with these problems every day, but the authors stress that there is a need for more research into the mechanism behind skin toxicity, and for more clinical studies to develop evidence-based guidelines.

Like all such documents, the consensus guidelines represent a compromise. While metronidazole, erythromycin, clindamycin and benzoyl peroxide are all recommended to treat the acneiform eruption, Segaeert, who is lead author, says his preference is to stick with metronidazole because, unlike the others, it is specially formulated for sensitive skin. His view is supported by the HER1/EGFR-inhibitor Rash Management Forum, which convened in New York in January 2004, and included dermatologists and oncologists from Canada, Germany, Italy, Spain and the US. They argue against the use of benzoyl peroxide, because it would aggravate the dry skin, and suggest a clinical trial to evaluate the use of topical antibiotics such as clindamycin.

The use of retinoids is another area of controversy. These are used as standard for normal acne and are reportedly used in France for treating EGFR inhibitor-related skin rash. The JDDG document keeps an open mind on these options, stating that “the use of oral retinoids in this setting remains experimental.”

DOS AND DON'TS

- Be prepared for skin side-effects; the acneiform eruption will probably peak at around two weeks, but can also flare up later. It can be alleviated but not cured by careful management. This is also true of longer-term side-effects such as dry skin, fissures on the fingers, toes and heels, inflammation around the nails, ulcers in the nose and mouth and vaginal dryness
- Keep out of the sun. Heat and humidity exacerbates the inflammation and too much sun can lead to hyperpigmentation in the affected areas.
- Wash skin and hair in lukewarm water, and not too frequently. Too much washing dries the skin, and the rash is not caused by dirt or infection (though these can cause complications)
- Use bath or shower oil or special skin-friendly soaps and shampoos rather than normal soaps, shampoos or gels, which can exacerbate dry skin problems – a good rule is to avoid anything that foams
- Wear shoes that don't press on your toes; take them off or wear slippers or open-toed sandals where possible
- Use moisturising cream to counter dry skin on the limbs, but avoid using it on areas affected by the acneiform eruption, as this can suffocate the skin and make the rash worse
- It's fine to use make-up, but stick to hypo-allergenic brands
- Don't worry about diet; it is not a factor
- For treatment of the rash, look for advice from your oncology team or a specialist dermatologist. General practitioners, pharmacists or dermatologists unfamiliar with the problem may recommend standard anti-acne treatments, many of which are unsuitable



This treatment algorithm for EGFR inhibitor-related skin reactions represents a consensus reached by oncologists and dermatologists from all over Europe. Some of the recommendations, such as the use of retinoids or benzoyl peroxide, remain controversial. Lead author Siegfried Segaert and the New York HER1/EGFR-inhibitor Rash Management Forum do not recommend their use

Source: S Segaert, J Tabernero, O Chosidow et al. The management of skin reactions in cancer patients receiving epidermal growth factor receptor targeted therapies. JDDG vol 8, p603, © Blackwells 2005

Segaert’s personal view is that all retinoids are inappropriate, being too irritating and without rationale. “They work on blackheads and whiteheads, which you have in acne, but not in EGFRi induced acneiform eruption.” This view also receives support from the HER1/EGFR-inhibitor Rash Management Forum, which states that there are no data to support the use of retinoids, and use is not advised as their skin-drying effects may exacerbate the rash.

Segaert also advises strongly against using the oral retinoid isotretinoin Accutane or Roaccutane, at least for now. Though it appears to be effective against EGFRi-associated rash, the drug is known to downregulate EGF receptor, and could thus diminish the target for the anti-cancer drug. It also causes side-effects that would compound other symptoms – dry skin, nail-fold inflammation, and a tendency to superinfection with *S. aureus*.

Some of these areas of controversy

are likely to remain – with doctors balancing the anti-rash effect against exacerbating the dry skin problem, according to their own preferences and the practice in their department. Other areas will hopefully be clarified through prospective clinical trials, such as the BABEL trial being carried out in Belgium, which is seeking to establish whether oral tetracycline in addition to topical therapy is more effective than topical treatment alone for cetuximab-induced acneiform eruption.

FROM GUIDANCE TO PRACTICE

One of the big challenges for effective management of skin problems is the different treatment approaches needed to cope with the variety of side-effects, at different stages, with varying severity and impact on the patient’s quality of life. Meeting this challenge requires a multi-disciplinary approach in which oncologist, dermatologist and specialist nurse all play a role, and also requires good and fre-

quent communication with the patient.

Teams working with EGFR inhibitors need to build a close collaboration with dermatologists who have expertise in this area, says Segaert. However, dermatologists do not normally need to be directly involved in caring for patients unless their rash is grade 3 or 4.

Preparing patients in advance for what is likely to happen to them is essential. Gasthuisberg nurse Liesbeth Lemmens suggests that oncologists should start by telling their patients: “We have a lot of experience with this skin toxicity. It can sometimes be severe, but we can treat it.” Illustrations showing where on the body the different problems are likely to appear are helpful, but she advises strongly against showing patients the close-ups of severe rash used in academic literature, which can be unnecessarily alarming.

Patients at Herlev University Hospital in Copenhagen, Denmark, are now given a ‘green card’ before starting their treatment. This details the sorts of symptoms that may develop, offers general advice on dos and don’ts, what sort of soaps, lotions and creams to use, and what additional treatments can be prescribed by the doctor. It encourages patients to report any side-effects that bother them.

At both Herlev and Gasthuisberg in Leuven, patients starting treatment with an EGFR inhibitor are routinely given a bag containing recommended lotions, creams, soaps, shampoos and so on. This means that patients can apply the treatments as soon as symptoms start to appear – or even before. Inge Nielsen, head nurse at the Herlev unit for experimental cancer treatment, says it is also very important psychologically: “The patient feels we care about them.”

Under the current experimental protocol for cetuximab, patients being treated in an adjuvant setting have to tolerate the drug for six months.

“We are absorbed in new treatments, without considering what it is doing to quality of life”

Patients with metastatic disease will be on EGFR-inhibitors until they stop responding. Knowing their oncology team understands the distress these side-effects can cause and is committed to helping alleviate the problem is likely to be important in helping patients stick with the treatment.

Lemmens remembers helping one young patient improve the appearance of her face sufficiently to attend a particularly important party. “We treated her with oral corticosteroids for a couple of days (though this is not standard care), and advised her on what cosmetics she could use, and she went to the party and she was happy.”

Giving patients a treatment break is difficult because little is known about how quickly the disease is likely to progress. When patients start to get really fed up, Lemmens sometimes tells them that skin rash tends to indicate that the cancer is responding well to the treatment. “That makes them feel better.” She says, however, that it is important to be careful about using that information, “You can’t say that from the start, because we do have patients who don’t have skin toxicity who also have a good response. And you need to check who might overhear. Is there a patient sitting nearby who has no toxicity at all?”

Under-reporting symptoms can also be a problem. Nielsen stresses that it is important to ask patients about each symptom every time you see them. Sometimes patients keep quiet because they are worried they may be taken off the treatment. Others suffer in silence or can’t face taking any more medicines or ointments.

“We have to ask the patients to take off their shoes and look at their feet, because they do not tell us if we don’t ask them. You need to ask very clearly: ‘Can I see your feet? What about your fingers? Do you take the pills we recommend? Are you using sun protection? How are your eyes? Can I look in your nose?’ Another thing that can be very irritating is vaginal problems for women. You have to ask them, because it is very difficult for the women to ask us about it. Those problems are more common than we even know, and we are not good at questioning women about it.”

This approach takes time, always a scarce resource in oncology departments. Developing a standard protocol for discussing side-effects and selecting treatment options is key to saving time while ensuring that all patients are cared for appropriately. The treatment algorithm published from the consensus conference (p20) is a good starting point. At Herlev, in addition to the ‘green card’ for patients, they have published an orange booklet that medical and nursing staff can use to identify grades of rash and other problems, and to select treatments.

Experience also helps speed up the process. Nielsen says, “In the beginning it took a lot of time for us, but now it is just part of the treatment to discuss the side-effects with the patient, and we don’t have to think so much about it.” She sees her patients every two weeks, and estimates that she needs an average of 30 minutes, with the greatest time usually needed before treatment and in the early weeks.

A similar point is made at Gasthuisberg by Van Cutsem. “It took me far longer in the past. It is important to be well organised. I was able to learn a lot from the dermatologist and he was able to learn a lot from us. Having strong nursing backup is very important. They can help instruct for some of the easy aspects, and give a lot of practical tips.”

Lemmens has worked alongside Van Cutsem for three years with patients who are on cetuximab and panitumumab as third-, second- or first-line treatments or taken as adjuvant treatment. She says that nurses play a key role with the patients. “You need the oncologist to prescribe the drugs, unguents and antibiotics and so on. And then there is the dermatologist who can advise patients if the oncologists are not sure what to do... with infections, with paronychia, for more specialised care. The nurses can be very helpful as far as the general recommendations are concerned – the dos and the don’ts. They can advise the patients weekly on what to do and what to take. They are a go-between between the physician and the patient.”

Weekly advice is, of course, easier if the patient has to visit the treatment centre that often, as is common with cetuximab. Panitumumab, however, tends to be administered fortnightly, so the oncology team has to think ahead and encourage patients to phone for advice. The tyrosine kinase inhibitors gefitinib and erlotinib are both administered orally, resulting in fewer visits to the treatment centre. Factoring in the need to control the side-effects is therefore particularly important here.

FILLING THE KNOWLEDGE GAP

As increasing numbers of patients are treated by EGFR inhibitors at more and more treatment centres, it is essential that existing knowledge and experience about managing the skin side-effects is rapidly disseminated. Segaert encourages oncologists to communicate with dermatologists, to learn about the side-effects, read the papers and go to presentations. He also says that many dermatologists need to get up to speed on how to manage this unique combination of problems.

Specialist nurses are in the front-line of advising patients and administering more general treatments, and they also need training – something the TARGET course run by the European Oncology Nursing Society is designed to do (<http://tinyurl.com/36dvbo>). Nielsen admits to feeling isolated when trying to develop a protocol at her own department at Herlev, and says that it is important for nurses to have the chance to get together, compare notes, and pass on their experience to others. Both she and Lemmens are painfully aware of the lack of evidence-based guidelines that they have to work with. The likelihood is that in six months or a year the advice they will be giving patients may be quite different from what they are saying today.

And generating this new knowledge is the second priority. Clinical trials involving EGFR inhibitors often include a translational element looking at the mechanism behind the skin changes. Early research into possible treatments targeted at this specific problem may be beginning to bear fruit; one promising strategy is to cancel the effect of the EGFR inhibitor specifically in the skin, while still allowing it to function against the cancer. A topical phosphatase inhibitor – vitamin K3 – which inhibits

enzymes that dephosphorylate the EGFR is currently in the early stages of development.

While waiting for a wonder drug, however, there is a lot that can be learned about how best to use existing treatments. Controversies over the use of retinoids, steroids, or the best time to start administering systemic anti-rash treatments such as tetracycline, need clarification through prospective clinical trials. Lemmens believes a great deal could also be learned by systematically sharing experiences between treatment centres, and floats the idea of setting up a website for this purpose.

There remains a big knowledge

gap about how the skin-effects of EGFR inhibitors impact on patients' lives. Including quality of life measures as a parameter in clinical trials is one of the main recommendations of the JDDG document on managing skin toxicities. It is also something Nielsen feels particularly strongly about.

“We are still too absorbed in just looking at what new treatment we can offer, without any consideration of what it is doing to patients' quality of life. We have to take into account how the patient is feeling. We shouldn't just look at a patient, make up our minds and treat them. We have to ask patients what they want from us.”

EGFR INHIBITORS

Two EGFR inhibitors are currently approved for use in Europe

- Cetuximab (Erbix): a monoclonal antibody approved for use in combination with irinotecan in patients with metastatic EGFR-expressing colorectal cancer when previous treatment including irinotecan has failed. This drug is also approved for use in patients with locally advanced squamous cell cancers of the head and neck, when it is given in combination with radiotherapy.
- Erlotinib (Tarceva): a tyrosine kinase inhibitor (small molecule) approved for use in patients with locally advanced or metastatic non-small-cell lung cancer after failure of at least one prior chemotherapy regimen.

Three additional EGFR inhibitors are currently approved in the US

- Gefitinib (Iressa): also a tyrosine kinase inhibitor approved for NSCLC. Approval was refused by EMEA on the grounds that survival benefit was insufficient across the trial population.
- Panitumumab (Vectibix): a fully human monoclonal antibody approved for use in metastatic colorectal cancer following standard chemotherapy. An application for marketing approval was submitted to EMEA in April 2006.
- Lapatinib (Tykerb): a dual ErbB2/EGFR inhibitor, approved by the FDA in March this year for patients with HER2-positive locally advanced or metastatic breast cancer who have received prior therapy with other cancer drugs, including an anthracycline, a taxane, and trastuzumab (Herceptin). An application for approval by EMEA was submitted last October.

Future directions

All the above EGFR inhibitors are being intensively investigated to gauge effectiveness in a variety of other indications, including pancreatic, renal cell and ovarian cancers, and at earlier stages and in different combinations. This includes combining with cytotoxics, with radiotherapy, and with other targeted drugs, such as bevacizumab (Avastin, which inhibits angiogenesis by targeting vascular endothelial growth factor – VEGF) or multi-kinase inhibitors such as sunitinib (Sutent) or sorafenib (Nexavar).