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Cutaneous Reactions to Anticancer Agents Targeting the Epidermal Growth Factor Receptor: A Dermatology-Oncology Perspective

M. E. Lacouture, MD[1]; B. L. Melosky, MD[2]

[1]SERIES Clinic, Department of Dermatology and Robert H Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
[2]Vancouver Centre, BC Cancer Agency, Vancouver, BC, Canada

ABSTRACT

The epidermal growth factor receptor (EGFR) is often overexpressed or dysregulated in solid tumors. Targeting the EGFR-mediated signaling pathway has become routine practice in the treatment of lung, pancreatic, head and neck, and colon carcinomas. Available agents with selected activity towards the EGFR include low molecular weight tyrosine kinase inhibitors, e.g., erlotinib (Tarceva®, Genentech BioOncology/ OSI Pharmaceuticals/ F. Hoffmann-La Roche) and monoclonal antibodies, such as cetuximab (Erbitux®, Bristol-Myers Squibb/ ImClone Systems/ Merck) and panitumumab (Vectibix®, Amgen). Their use is anticipated to increase for treating other solid tumors that are dependent on this pathway for growth and proliferation. Health Canada and the US FDA have approved erlotinib for the treatment of advanced non-small cell lung carcinoma (NSCLC). It has also been approved in the US for use against pancreatic cancer in combination with gemcitabine (Gemzar®, Eli Lilly). Cetuximab and most recently panitumumab (Vectibix™, Amgen/ Abgenix) were approved by the US FDA for metastatic colorectal carcinoma. Cetuximab is also approved in the US for head and neck squamous cell carcinoma. The safety profile for this class of drugs is unique, with virtually no hematological toxicity, but frequent cutaneous and gastrointestinal side-effects. Although there is a dearth of randomized trials addressing treatment of the dermatological side-effects, some basic principles of management have been agreed upon and can likely improve patient compliance and decrease inappropriate dose reduction, which may negatively influence the antitumor effect.

Key Words: *Anticancer agents, epidermal growth factor receptor, EGFR inhibitor, monoclonal antibodies, tyrosine kinase inhibitors, cutaneous reactions*

The human epidermal growth factor receptor (HER1/EGFR) is a transmembrane glycoprotein of the tyrosine kinase growth factor family that is expressed in many normal human tissues. It is finely regulated to control cell growth and proliferation. In many cancers, this growth factor is dysregulated and overexpressed, and this overexpression is common in many solid tumors, such as colorectal (65-75%), head and neck (90%), and lung (60%-90%) carcinomas. It correlates with increased metastasis, reduced survival, and a poor prognosis.[1]

Overexpression can result in uncontrolled cell growth, proliferation, angiogenesis and metastases. This growth factor can be successfully blocked by antibodies against the extracellular domain of the receptor, or small molecule inhibitors directed against the intracellular tyrosine kinase domain. Whereas a blockade of the receptor in tumors leads to beneficial effects, in skin and appendages this leads to undesirable reactions, including a papulopustular eruption, hair growth disorders, periungual and nail plate abnormailities, xerosis, and pruritus.

Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitors are small molecules given orally that target the EGFR receptor. By blocking the intracellular ATP binding site, phosphorylation cannot be completed, thereby inhibiting the signaling cascade that activates growth and proliferation factors.

In 2004, erlotinib received US FDA approval for patients with advanced NSCLC who have failed at least one prior chemotherapy regimen. This was based on the results of a pivotal phase III trial (BR.21), in which erlotinib prolonged median survival by 42.5% over best supportive care (6.7 months vs. 4.7 months; P <0.001) in patients after one or two prior chemotherapy regimens.[2]

The side-effects reported in this trial included diarrhea (50%) and rash (75%). Typically, the rash developed about 7–10 days after the start of treatment, affecting the skin above the waist, and resolving spontaneously without treatment. In most patients, the rash was mild (grade 1 or 2); only 8% of patients had grade 3 rashes, and <1% had a grade 4 rash.[2] For grade 3 and 4 rashes, the protocol recommended stopping the drug for 7–10 days, then resume at 30% dose reduction. Importantly, subsequent analysis suggested a positive correlation of the rash to response and survival.[2]

Monoclonal Antibodies

Monoclonal antibodies against the epidermal growth factor are given intravenously. By this action, the epidermal growth factor produces a similar end result as tyrosine kinase inhibitors. In 2004, the FDA approved cetuximab as a combination treatment with irinotecan (Camptosar®, Pfizer) for the treatment of patients with metastatic colorectal cancer. This was based on a randomized study that showed the combination of cetuximab and irinotecan had a response rate of 22.9 % and delayed tumor growth by 4.1 months.[3] Rash was observed in 87% of these individuals.

Panitumumab, a fully humanized monoclonal antibody, is also approved for this same indication with a similar benefit in progression-free survival.[4] Cetuximab has also shown an improvement in survival when given with radiation to patients with head and neck cancer.[5] Like the tyrosine kinase inhibitors, a correlation of response and survival to those who experienced the highest grade of rash has been shown.[2]

Pathophysiology of Skin Toxicities

EGFR is expressed in the basal layer of the epidermis. Its roles include stimulation of epidermal growth, inhibition of differentiation, and acceleration of wound healing. Effects of EGFR inhibition include impaired growth and migration of keratinocytes, and inflammatory chemokine expression by these cells. These effects lead to inflammatory cell recruitment and subsequent cutaneous injury, which accounts for the majority of symptoms, including tenderness, papulopustules, and periungual inflammation.[6] Histologic specimens reveal a mixed inflammatory infiltrate surrounding the upper areas of the dermis, follicular rupture, and epithelial acantholysis. Direct immunofluorescent studies show a nonspecific pattern of staining. Inhibition of mitogen activated protein kinase (MEK) by pharmacological methods, a downstream effector in the EGFR pathway, also leads to papulopustules, suggesting a mechanism-based effect.[7] Similar inflammatory events may also account for the periungual inflammation and onycholysis, whereas abnormalities in keratinocyte differentiation i.e., premature expression of keratin 1 and STAT 3, may explain the impaired stratum corneum leading to xerosis and pruritus.[7]

Description of Dermatological Toxicities

The effects of EGFR inhibitors on epidermal-derived tissue includes a papulopustular eruption, dry skin, pruritus, ocular and nail changes.[6] Common terms used to describe the rash are acneiform skin reaction, acneiform rash, acneiform follicular rash, acne-like rash, maculopapular skin rash, and monomorphic pustular lesions. However, the term papulopusular reaction is a more accurate description. The rash may be triggered by sun exposure,[8] and develops in the following phases: sensory disturbance, erythema, and edema (week 1); papulopustular eruption (week 2); crusting (week 4); and, if the rash is treated successfully, a background of erythema and dry skin can be seen in areas previously affected by the papulopustular eruption (weeks 4–6).[7] Other events such as pruritus, erythema, and paronychial inflammation

Agent	Specificity	Type	Indication	Sponsor
Erlotinib (Tarceva®)	Reversible EGFR/ HER1	TKI	NSCLC and in combination with gemcitabine for pancreatic cancer	Genentech Inc/ OSI Pharmaceuticals Inc/ F. Hoffmann-La Roche
Cetuximab (Erbitux®)	EGFR/ HER1	mAb chimeric IgG1	CRC and SCCHN with radiation	Bristol-Myers Squibb/ ImClone Systems Inc/ Merck
Gefitinib (Iressa®)	Reversible EGFR/ HER1	TKI	NSCLC May 2003, now with restricted availability.[1]	AstraZeneca
Panitumumab (Vectibix®)	EGFR/ HER1	mAb humanized IgG2	Metastatic CRC	Amgen/Abgenix

Table 1: FDA approved tyrosine kinase inhibitors (TKIs) and monoclonal antibodies (mAbs). NSCLC = non-small cell lung cancer; SCCHN = squamous cell carcinoma of the head and neck; CRC = colorectal carcinoma; IgG1 = gamma G Immunoglobulin; EGFR = epidermal growth factor receptor; HER1= human epidermal growth factor receptor type 1.

associated with the lateral nail folds of the toes and fingers can occur. Paronychia may occur after a longer period of treatment.

Treatment of Rash

In the randomized trials where the primary endpoint was survival and response, rash treatment was often vague and not well documented. As well, there is difficulty in interpreting these trials because the rash was graded according to the National Cancer Institute (NCI) criteria (NCI CTC criteria version 2.0 and 3.0) and may not accurately reflect the clinical situation.[9] A more accurate grading system is urgently needed, and this is one of the major tasks of the Skin Toxicity Study Group of the Multinational Association of Supportive Care in Cancer (www.mascc.org).

The specific treatment algorithms for rashes caused by EGFR inhibitors vary widely throughout different centers that use these agents in their clinics. Nonetheless, some basic principles may apply. In the following section, management recommendations from the dermatology-based SERIES (Skin and Eye Reactions to Inhibitors of EGFR and kinaseS) clinic[10] (Figure 1, see page 5) will be presented along with those utilized in the BC Cancer Agency Oncology Department (Table 2). Both of these regimens are currently being investigated in clinical trials.

Management Recommendations

Patients need to be educated on the importance of taking oral TKIs on an empty stomach. Furthermore, patients should be instructed to use an alcohol-free emollient cream applied twice daily, preferably to their entire body. Physicians should also recommend that patients use a broad spectrum sunscreen, since sun exposure may aggravate their rash.[8]

Mild reactions (NCI-CTC grade 1) are generally localized with no associated physical symptoms. Treatment options include topical low-medium potency corticosteroids or calcineurin inhibitors (TCIs) (i.e., pimecrolimus [Elidel®, Novartis]; and tacrolimus [Protopic®, Astellas Pharma]), all of which are able to inhibit inflammation. TCIs do not cause the side-effects attributed to corticosteroids, such as skin atrophy, acne/rosacea-like reactions, and dyspigmentation. However, their use is hampered by the development of pruritus and burning in a subset of patients. Other options include the addition of clindamycin 1% gel to hydrocortisone 1% (B. M., unpublished data), and the use of oral semisynthetic tetracyclines (i.e., doxycycline or minocycline). The EGFR inhibitor should be continued while the rash is being treated.

Moderate reactions (NCI-CTC grade 2) are more disseminated and can include symptoms such as tenderness or pruritus. The recommended treatment is hydrocortisone 1% or 2.5% cream +/- clindamycin 1% gel, as well as a 4-week course of an oral tetracycline antibiotic, such as doxycycline 100mg or minocycline 100mg twice daily.

Severe reactions (NCI-CTC grade 3) are generalized with major symptoms affecting activities of daily living and are intolerable to the patient. In addition to the above measures, a short course of oral corticosteroids may be administered (i.e., methylprednisolone [Medrol® dose pack, Pfizer]). Although histological findings suggest that the papulopustular reaction has an inflammatory component, the use of topical/ oral corticosteroids is based on empirical data. Alternatively, a temporary 7–10 day discontinuation of the drug involved is recommended with subsequent reintroduction at a lower dose according to the product monograph. Treatment with both a steroid cream and oral tetracycline as per moderate rash is encouraged during the interruption period. Oral isotretinoin (Accutane®, Roche) may be considered for patients who do not respond to the above measures. Therapy with low dose (10-20mg daily) oral isotretinoin must be employed with caution, as it may exacerbate xerosis and paronychia, all of which may be present with EGFR inhibitor use. Thus, oral isotretinoin should only be considered when other antitoxicity interventions have failed and a positive antitumor response is documented, making it imperative to maintain the patient on antiEGFR therapy.

Rashes on the Scalp

The rash may be successfully treated with the basic principles above, but often patients can develop lesions and

Severity of Rash	Treatment Protocol
Mild	Topical clindamycin 2%, with hydrocortisone 1% in lotion base applied twice-daily.
Moderate	Topical clindamycin 2%, with hydrocortisone 1% in lotion base applied twice-daily AND oral minocycline 100mg twice-daily for a minimum of 4 weeks and continuing thereafter as required, until resolution of the rash by one severity grade. Scalp lesions will be treated with a topical lotion clindamycin 2%, triamcinolone acetonide 0.1% in equal parts of propylene glycol and water.
Severe	Stop erlotinib therapy for 1 week and restart at 100mg once-daily. Treatment of rash with topical clindamycin 2%, with hydrocortisone 1% in lotion base applied twice-daily AND oral minocycline 100mg twice-daily for a minimum of 4 weeks and continuing thereafter as required. Scalp lesions will be treated with a topical lotion clindamycin 2%, triamcinolone acetonide 0.1% in equal parts of propylene glycol and water until resolution.

Table 2: BCCA EGFR Inhibitors: Rash protocol. Note: Erlotinib dose re-escalation is optional based on discretion of physician and improvement of rash by one grade.

plaques on the scalp. Scalp lesions can be treated with topical clindamycin 2% plus triamcinolone acetonide 0.1% in equal parts of propylene glycol and water until resolution.

Management of Dermatological Toxicities Other Than Rash

Due to the lower frequency and visibility of additional toxicities when compared to rash, management recommendations and uncontrolled reports are limited. Nail changes are usually mild, but like the rash, may be severe and symptomatic. Oral doxycycline may be effective along with topical corticosteroids,[11] but in resistant cases, intralesional corticosteroid injections or removal of the nail plate may be beneficial.[12] Dry skin in the trunk and extremities is very common. Fragrance free creams and ointments are preferred over lotions, which may contain alcohol. For scaling and hyperkeratosis, ammonium lactate and urea containing preparations are also useful, but they should be used with care because of greater skin sensitivity. Eyelash growth can be seen when epidermal growth factors are given for a prolonged period of time. Cutting the eyelashes intermittently to a shorter length can add to patient comfort.

Conclusions

Currently, the EGFR pathway is targeted for cancer treatment using oral tyrosine kinase inhibitors or intravenous monoclonal antibodies. These agents have become standard treatment in both lung and colorectal carcinomas and their usage will only gain in frequency as they move into the treatment of other solid tumors and other indications like adjuvant therapy following curative resection. The side-effects shared by this class of drugs primarily affect the skin and appendages. Rash management is a key factor in patient tolerance and compliance. Severe rash and dose reductions can be avoided with proactive/early intervention and proper education directed to both patient and physician.

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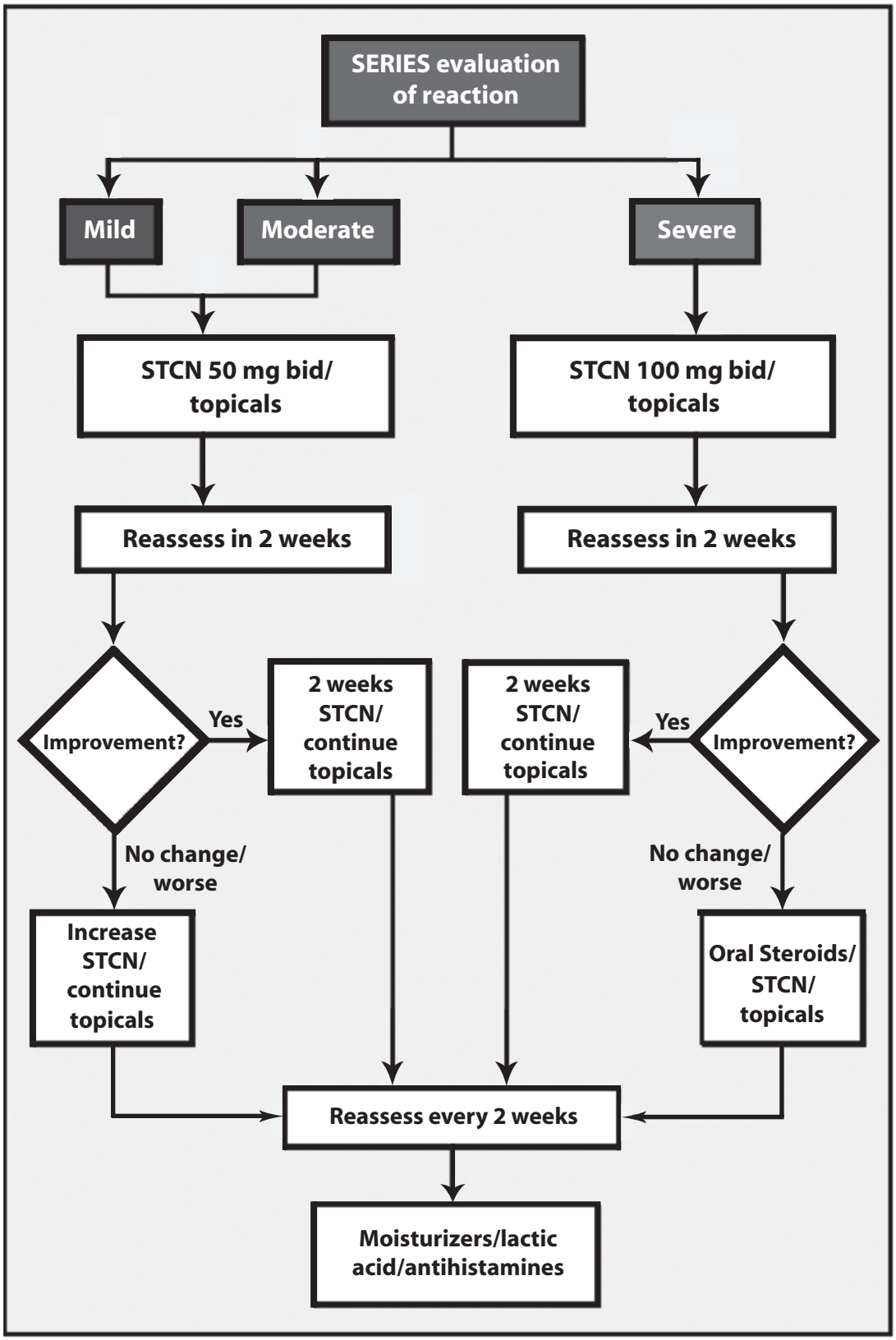

Figure 1: From page 1 article *Cutaneous Reactions to Anticancer Agents Targeting the Epidermal Growth Factor Receptor: A Dermatology-Oncology Perspective*. SERIES Management algorithm for papulopustular reactions to EGFR inhibitors (from Lacouture et al., *J Supportive Oncol*,[10] reprinted with permission). Severity of papulopustular reaction is graded based on clinical findings and symptoms (mild/moderate, severe). Abbreviations: EGFR=epidermal growth factor receptor inhibitor; SERIES=Skin and Eye Reactions to Inhibitors of EGFR and kinaseS; STCN= semisynthetic tetracyclines (doxycycline); topicals (steroids or calcineurin inhibitors); dose mod=EGFR inhibitor dose reduction or interruption; isotretinoin=low doses (10-20mg a day) isotretinoin.

Rituximab: A B-Cell Depletion Therapy for Dermatologic Disease

V. Prajapati; P. R. Mydlarski, MD, FRCPC

Division of Dermatology, Department of Medicine, University of Calgary, Calgary, AB, Canada

ABSTRACT

Rituximab (Rituxan®, Genentech/ Biogen Idec) is a genetically engineered chimeric murine/human monoclonal antibody directed against CD20, a B lymphocyte-specific antigen. Initially approved for the treatment of relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma (NHL), rituximab has been increasingly used to treat a variety of immune-mediated and autoimmune diseases. While anecdotal case reports recommend its "off-label" use in dermatology, randomized clinical trials are required to firmly establish the safety and efficacy of this emerging biologic therapy.

Key Words: *Rituximab, Rituxan®, immune skin disease, monoclonal antibody*

In 1994, Reff and colleagues developed a chimeric murine/human anti-CD20 monoclonal antibody which induced the rapid depletion of $CD20^+$ B lymphocytes *in vivo*.[1] By 1997, rituximab (Rituxan®) was approved by the US FDA for the treatment of relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma (NHL). Originally developed for the treatment of B cell malignancies, rituximab has since been used to treat a variety of immune-mediated and autoimmune diseases (i.e., rheumatoid arthritis, systemic lupus erythematosus, and idiopathic thrombocytopenic purpura). Herein, we review the potential applications and limitations of rituximab use in dermatology.

Mechanism of Action/ Pharmacology

Rituximab is an immunoglobulin G1 (IgG1) kappa monoclonal antibody composed of a murine variable region (Fab portion) that is fused onto a human constant region (Fc portion). The Fab portion binds specifically to the CD20 antigen, located exclusively on the surface of pre-B and mature B lymphocytes. Once bound, the Fc portion of rituximab recruits immune effector cells to help mediate cell lysis of the $CD20^+$ B lymphocytes via 3 possible mechanisms:

- complement-dependent cytotoxicity (CDC)
- antibody-dependent cell-mediated cytotoxicity (ADCC)
- apoptosis.[1]

The exact contribution of each mechanism remains unclear, and different mechanisms may prevail in different diseases.[2]

The use of rituximab results in the rapid depletion of both normal and malignant $CD20^+$ B lymphocytes in the peripheral blood and, to a lesser extent, the lymph nodes.[1] The CD20 antigen is not expressed on the surface of hematopoietic stem cells or pro-B cells; thus, the capacity of these precursor cells to regenerate the B lymphocyte population remains intact.[1] As the majority of plasma cells fail to express the CD20 antigen, plasma cells are generally spared and serum immunoglobulin levels tend not to fall dramatically.[3] Here lies the selective advantage of rituximab.

Pharmacokinetics

In patients receiving rituximab intravenously, serum levels are dose-proportional, correlate with patient response to therapy, and increase with each successive infusion.[3-5] The half-life of rituximab is also proportional to the dose, increases with each subsequent infusion, and varies greatly from patient to patient. The wide variability in elimination half-lives may reflect differences in tumor burden and changing $CD20^+$ B cell populations with repeated administrations. Though the mechanisms involved in the metabolism and elimination of rituximab are not fully understood, it is postulated that rituximab is degraded nonspecifically in the liver and excreted in the urine.[6]

Dosage

In adults, the standard dosing schedule for rituximab is $375mg/m^2$ given intravenously once per week for 4 consecutive weeks. Premedication with an antipyretic (i.e., acetaminophen) and an antihistamine (i.e., diphenhydramine) should be administered prior to and throughout each infusion to reduce the likelihood of infusion-related reactions.[7]

In order to minimize the risk of tumor lysis syndrome, bulky tumors require higher doses of rituximab to be staggered over several weeks. As there is a limited number of $CD20^+$ B cells in the normal immune system, an alternate dosing regimen was developed for patients with rheumatoid arthritis (RA). In RA patients, rituximab may be given as two-1000mg intravenous infusions separated by 2 weeks.[8]

Recently, a few cases of primary cutaneous B-cell lymphoma have been treated successfully with intralesional injections of rituximab. The dose ranged from 1-3mL of a 10mg/mL solution and variable numbers of injections were administered.[9-12]

Rituximab is currently supplied at a concentration of 10mg/mL in either 100mg (10mL) or 500mg (50mL) single-use vials.[7]

Adverse Effects/ Drug Interactions

Rituximab is generally well tolerated, though most patients experience mild-to-moderate infusion-related reactions with their first treatment. The most common symptoms include fever (48%), chills (32%), weakness (18%), nausea

(17%), headache (13%), pruritus (12%), and rash (11%).[7] The symptoms are usually reversible by temporarily discontinuing the infusion and providing symptomatic relief. Infusion-related side-effects tend to diminish or disappear with subsequent infusions.

Severe and potentially fatal adverse events, though rare, have been associated with rituximab therapy. These include severe infusion-related reactions, tumor lysis syndrome, mucocutaneous reactions such as Stevens-Johnson Syndrome (SJS), anaphylaxis, serious pulmonary events, cardiac arrythmias, renal failure, hematological abnormalities, bowel obstruction/perforation, and significant infections, such as bacterial sepsis, reactivation of hepatitis B with fulminant hepatitis, and progressive multifocal leukoencephalopathy (PML).[7] With regard to PML, a recent safety warning was issued by the US FDA regarding the development of this potentially fatal viral infection in the central nervous system (CNS) in 2 patients with systemic lupus erythematosus (SLE) who were being treated with rituximab.[13] Patients should be urged to seek prompt medical attention if they develop any new neurological symptoms (i.e., changes in vision, balance, or cognition).

The use of rituximab in children and in patients with renal or hepatic failure has not been studied extensively. Rituximab should be avoided during pregnancy unless the potential benefit justifies the potential risk to the fetus (Pregnancy Risk Category C). As human IgG is excreted in breast milk, lactating mothers should be advised to discontinue nursing until circulating blood levels are no longer detectable. Though there have been no formal drug interaction studies performed with rituximab, the concomitant use of rituximab and cisplatin should be avoided as this combination has been associated with renal failure.[7]

Clinical Uses

Although approved for the treatment of relapsed or refractory low-grade or follicular NHL, the list of "off-label" indications for rituximab continues to grow. Case reports and small case series document its use in the dermatologic literature. Potential indications are listed in Table 1, and select dermatologic diseases are reviewed.

Primary Cutaneous B-Cell Lymphoma (PCBCL)

In a recent review, more than 40 individual cases of PCBCL were treated with rituximab intravenously.[2] In the two largest case series, 10 patients were enrolled in each study. The overall response rate was 70% (20% complete response, 50% partial response) in the first study and 90% (70% complete response, 20% partial response) in the second study.[14,15]

Nineteen cases of PCBCL treated with intralesional rituximab were found in the literature.[9-12,16] A complete response was seen in 84% of patients, while a variable response was seen in the remaining 16%. Relapse rates were found to be higher with intralesional therapy when compared with standard systemic therapy.

Dermatologic Disease
Primary cutaneous B-cell lymphoma
Immunobullous disease
Pemphigus vulgaris
Pemphigus foliaceus
Paraneoplastic pemphigus
Bullous pemphigoid
Mucous membrane pemphigoid
Epidermolysis bullosa acquisita
Chronic graft versus host disease
Dermatomyositis
Systemic lupus erythematosus
Vasculitis
Small vessel vasculitis
Hypocomplementemic urticarial vasculitis
Antineutrophil cytoplasmic antibody-vasculitis
Cryoglobulinemia
Schnitzler syndrome
Waldenstrom's macroglobulinemia
Angioedema
Vitiligo

Table 1: Potential dermatological uses of rituximab

Pemphigus Vulgaris (PV)

Multiple case reports suggest that rituximab is an effective treatment option for PV. In a recent review of 18 patients with refractory PV, 3 patients (17%) experienced complete remission (no further therapy required), 4 patients (22%) experienced clinical remission (healing of all lesions but further therapy required), and 11 patients (61%) experienced partial remission.[17] The standard course of rituximab was administered in all but 2 patients who received additional infusions. Serious infections occurred in 4 of the 18 patients, of which 1 was fatal. Notably, patients were allowed to remain on concomitant immunosuppressive therapy.

In 11 patients with extensive, recalcitrant PV, efficacy was noted using a combination of rituximab and intravenous immunoglobulin (IVIG).[18] Rituximab (375mg/m^2) was administered once weekly for 3 weeks and followed by an infusion of IVIG (2g/kg) in the fourth week. The cycle was repeated once and, upon completion of the induction therapy, monthly rituximab and IVIG infusions were given for 4 consecutive months. Of the 11 patients, 9 patients had a clinical remission lasting between 22–27 months; no serious adverse events were noted. Taken together, the data suggest that rituximab may be effective for patients with severe, refractory PV.

Other Immunobullous Diseases

Case reports document the successful use of rituximab in other immunobullous diseases, including: pemphigus foliaceus, paraneoplastic pemphigus, bullous pemphigoid, mucous membrane pemphigoid and epidermolysis bullosa acquisita.[19-24] In most cases, complete remission was achieved with the standard therapeutic regimen. However,

several cases of PNP have shown resistance to rituximab therapy.

Chronic Graft Versus Host Disease (CGVHD)

The use of rituximab in the treatment of refractory CGVHD has been documented in multiple case series with mixed results. In one case series, 8 patients with extensive CGVHD were treated with the standard course of rituximab.[25] Four of these patients (50%) responded to rituximab therapy whereas the other 4 patients (50%) were nonresponders. In the largest series of 21 patients with steroid-refractory CGHVD, the overall response was 70% and included 2 patients who experienced a complete remission.[26] In these patients, rituximab facilitated a statistically significant reduction in the median dose of steroid use from 40mg/day to 10mg/day ($p<0.001$). A steroid-sparing effect was therefore demonstrated in patients with CGVHD.

Dermatomyositis (DM)

In an open-label pilot study of 6 patients with longstanding refractory DM, patients received four weekly intravenous infusions of rituximab at a dose of 100mg/m^2 (three patients) or 375mg/m^2 (three patients).[27] All patients experienced marked clinical improvement in both cutaneous and muscle disease. Overall, rituximab was well tolerated in this patient group and no major adverse events were reported.

In another study, three patients with refractory DM experienced marked clinical improvement of their cutaneous disease.[28] In this small cohort, the heliotrope rash and the violaceous poikiloderma were most responsive to therapy.

Other Dermatologic Disease

Rituximab has been shown to benefit other dermatologic conditions including systemic lupus erythematosus (SLE), cryoglobulinemia, Waldenstrom's macroglobulinemia, Schnitzler syndrome, vitiligo, angioedema as well as cutaneous vasculitides such as small vessel vasculitis, hypocomplementemic urticarial vasculitis and antineutrophil cytoplasmic antibody-associated vasculitis.[21,29-31]

Conclusion

Though approved for the treatment of low-grade or follicular NHL, rituximab has demonstrated therapeutic efficacy in a variety of recalcitrant immune-mediated and autoimmune skin disorders. Few therapeutic failures have been described, possibly resulting from long-lived CD20$^-$ plasma cells capable of producing pathogenic autoantibodies. In most patients, rituximab is safe and tolerable with infusion-related reactions and infectious complications dominating the adverse-event profile. Clinical trials with long-term follow-ups are warranted to firmly establish the efficacy, tolerability and dosing of rituximab in the treatment of dermatologic disease.

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Class	Name/Company	Approval Dates and Comments
Dermal Filler	**Hyaluronic Acid Gel Particles** *PERLANE*® Medicis	The US FDA approved this dermal filler in May 2007 for implantation into the deep dermis to superficial subcutis for the correction of moderate-to-severe facial folds and wrinkles, such as nasolabial folds.
Vaccine	**Cervical Cancer Vaccine** *Cervarix*® GlaxoSmithKline	The Therapeutic Goods Administration of Australia approved this vaccine in May 2007 for the prevention of cervical cancer and precancerous lesions associated with the most common cancer-causing human papillomavirus types in females 10 to 45 years of age.
Vaccine	**Vaccinia Immune Globulin Intravenous (Human)** Cangene	The Biologics and Genetic Therapies Directorate of Health Canada approved this vaccine in May 2007 for counteracting certain complications associated with smallpox vaccination.
Antihistamine	**Levocetirizine Dihydrochloride** *Xyzal*® UCB/ sanofi-aventis	The US FDA approved this new once-daily prescription antihistamine in May 2007 for the relief of symptoms associated with seasonal and perennial allergic rhinitis and uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children >6 years of age.
Biologics	**Infliximab** *Remicade*® Centocor/ Schering-Plough	The European Commission approved a new indication for this biologic in June 2007 allowing for the treatment of severe, active Crohn's disease in pediatric patients 6-17 years of age who have not responded to conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy, or who are intolerant to, or have contraindications for, such therapies.

Drug News

Warning Letter	The US FDA sent out a warning letter to DUSA Pharmaceuticals in April 2007 about an advertisement for Levulan® Kerastick® for topical solution, stating that it was false or misleading because it presents efficacy claims for this product, but omits and minimizes the risks associated with the use of the drug, broadens the indications and overstates its efficacy. DUSA was instructed to immediately cease the dissemination of this advertising material. They were also asked to submit a comprehensive plan of action to disseminate truthful, non-misleading and complete corrective messages about the issues discussed in this letter to the audiences that received the promotional materials.
Focal Dermal Hypoplasia	According to an article published in a recent issue of *Nature Genetics**, researchers have identified the gene that accounts for most cases of Goltz syndrome, a rare skin disorder also known as focal dermal hypoplasia, that can also affect bone and eye development. The cases appear to result from a defect in the gene known as PORCN, which is active in the embryo and fetus, creating proteins that are important in the development of the skin, skeleton and eyes. The researchers believe mutations in the PORCN gene cause at least 75% of Goltz syndrome cases. *Wang X, et al. *Nat Genet* 39(7):836-8(2007 Jul).

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