

Systemic Retinoids: Chemoprevention of Skin Cancer in Transplant Recipients

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ABSTRACT

Solid organ transplant recipients (OTRs) have an increased incidence of skin cancer, resulting in significant morbidity and mortality post-transplantation. Chemoprevention strategies are focused on reducing and delaying the development of skin cancer in these patients. Although systemic retinoids are widely used in OTRs, few randomized controlled trials have been performed. Limited data suggest that acitretin may have a beneficial role in high-risk OTRs. Since rebound flares occur upon discontinuation of retinoids, chemoprevention should be viewed as a lifelong therapy. Further studies are required to establish the efficacy and long-term safety of systemic retinoids as chemopreventive agents for high-risk transplant recipients.

Key words: basal cell carcinoma, BCC, chemoprevention, organ transplantation, SCC, squamous cell carcinoma, skin cancer, systemic retinoids

Non-melanoma skin cancers (NMSC) are the most common human cancers worldwide. In Canada, the estimated incidence of NMSC is approximately 75,000 cases annually.¹ Though basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs) represent the two major types of NMSC, the term also encompasses Merkel cell carcinomas, cutaneous lymphomas, adnexal tumors, and other primary cutaneous neoplasms. Risk factors for the development of NMSC include ultraviolet radiation, immunosuppression, and chronic inflammation, thus supporting the interplay of the immune system in cancer development.^{2,3} Chemical carcinogens, other forms of radiation, infection with oncogenic strains of the human papilloma virus, and certain genodermatoses are additional known risk factors.^{2,3} Several complex genotypic, phenotypic, and environmental factors contribute to the pathogenesis of NMSC. Although cumulative sun exposure is the main risk factor for skin cancer development, further studies are required to fully understand the process of cutaneous oncogenesis.^{4,5}

The high incidence of skin cancer after solid organ transplantation is well recognized. In organ transplant recipients (OTRs), the risk of SCC development is 64 to 250 times greater than in the general population.⁶⁻⁸ While the overall metastatic rates for SCCs range from 2% to 10%, rates of up to 47% have been reported.⁹ Further, the incidence of SCCs to BCCs is inverted in OTRs at a ratio of 4:1.¹⁰ Skin cancers occur at a younger age of onset, often three to five years after transplantation.¹⁰

Surgical excision with predetermined margins remains the mainstay of therapy for most NMSCs. Of the non-invasive treatment options, only imiquimod and photodynamic therapy

have established efficacy in the treatment of select NMSC subtypes. Given the high incidence of NMSC in OTRs, chemopreventive therapies have been used to reduce and delay the development of skin cancer.¹⁰⁻¹² Herein, we review the literature on retinoid chemoprevention in organ transplant recipients.

Mechanisms of Action

Retinoids, natural and synthetic derivatives of vitamin A, are protective against a variety of cancers.¹³ They exert their physiologic effects by binding specific nuclear receptors.¹⁴ These receptors belong to a superfamily of glucocorticosteroid, thyroid hormone, vitamin D and peroxisome proliferator-activated receptors.¹⁵ There are two classes of retinoid nuclear receptors, the retinoic acid receptors (RARs) and the retinoid X receptors (RXRs).¹⁵ Each receptor family has three isoforms (α , β , and γ) which are encoded by separate genes.¹⁵ While RARs form heterodimers with RXRs, RXRs may form homodimers with RXRs or heterodimers with RARs, vitamin D₃ receptors or thyroid hormone receptors.¹⁵ In turn, these dimers act as ligand-dependent transcription factors for genes containing a retinoic acid response element (RARE).¹⁶ To date, over 500 genes have been reported to be regulatory targets of retinoids.¹⁷

The mechanism by which retinoids have a chemopreventive effect for skin cancer remains largely unknown. Several different mechanisms may be involved, including: immunomodulation, induction of apoptosis, effects on cell cycle control, inhibition of ornithine decarboxylase, inhibition of cellular proliferation and keratinization, and promotion of cellular differentiation.¹⁸ Experimental data suggest

that retinoids exert their effects during the promotion and progression stages of carcinogenesis.¹⁹ The pharmacology of specific retinoids is reviewed in Table 1.²⁰

Efficacy

The role of systemic retinoids in skin cancer chemoprevention was first established in patients with xeroderma pigmentosum.^{21,22} By the late 1980s, Shuttleworth et al. studied the efficacy of etretinate in preventing skin cancer in renal transplant recipients.²³ Although systemic retinoids are widely used in OTRs, few randomized controlled trials have been performed. Each trial has varying limitations, including small sample sizes. To date, the majority of studies on retinoid chemoprevention consist of case series.

While several case series support the efficacy of etretinate in the chemoprevention of NMSCs in OTRs, there are no clinical trials to validate these findings.²³⁻²⁶ Similarly, only a single case report supports the use of isotretinoin.²⁷ The best available evidence suggests that acitretin may be beneficial for high-risk OTRs.

In a prospective, open, randomized, cross-over trial, George et al. evaluated the efficacy of acitretin, a second generation retinoid, on NMSC development in renal transplant recipients.²⁸ Acitretin (25 mg per day) was administered to 14 patients, while nine patients received no therapy. Cross-over occurred at one year, and only 47.8% of patients completed the two-year trial. The number of SCCs observed in patients on acitretin was significantly lower than that in the drug-free period ($p = 0.002$). A similar, yet not significant, trend was observed for BCCs. In one patient, a severe rebound in SCC development occurred upon discontinuation of acitretin. Poor drug tolerability resulted in a high withdrawal rate.

Bouwes Bavinck et al. carried out a randomized, double-blind, placebo-controlled trial to study the effect of acitretin (30 mg per day) on NMSC development in renal transplant recipients.²⁹ All patients had ten or more keratotic skin lesions on the hands and forearms. During the six-month treatment period, two of 19 patients (11%) in the acitretin group reported a total of two new SCCs. In the placebo group, nine of 19

patients (47%) developed a total of 18 new SCCs ($p = 0.01$). The relative decrease in the number of keratotic skin lesions in the acitretin group was 13.4%, as compared to a relative increase of 28.2% ($p < 0.01$) in the placebo group. A relapse in keratotic skin lesions and skin cancers was noted upon discontinuation of therapy.

In a randomized, controlled, open-label trial, 26 renal transplant recipients were assigned randomly to two different one-year treatment protocols with acitretin.³⁰ Thirteen patients were treated with acitretin 0.4 mg/kg/day and 13 patients received acitretin 0.4 mg/kg/day during the first three months followed by 0.2 mg/kg/day for the remaining nine months. At nine different time points, the number of actinic keratoses and tumors were counted. The erythema and thickness of the lesions, as well as the severity of side-effects, were scored. In both groups, the number of actinic keratoses decreased by nearly 50%, but the number of new malignant tumors during the study year was similar to the pre-treatment period. Thickness of the keratoses decreased significantly in both groups. The frequency of mucocutaneous side-effects, such as cheilitis, excessive peeling of the skin, and hair disorders, resulted in significant dose reductions (only three of the 14 patients maintained acitretin at a dose of 0.4 mg/kg/day).

In a retrospective before-after study, Harwood et al. evaluated the efficacy of acitretin in the chemoprevention of SCCs.³¹ A total of 32 OTRs received acitretin (0.2 mg to 0.4 mg/kg/day) for one to 16 years. The number of SCCs developing annually during retinoid therapy was compared to the number of SCCs during the 12-month pre-treatment period. A statistically significant reduction in SCCs was noted in the first ($p = 0.006$), second ($p < 0.001$), and third ($p = 0.02$) years post-treatment.

Adverse Effects

The major limitation to the use of retinoids is poor tolerability.¹¹ In OTRs, mucocutaneous side-effects (i.e., cheilitis, xerosis, skin peeling, photosensitivity, and alopecia), headaches, and dyslipidemia frequently result in dose reductions.^{10,11,18} As dyslipidemia has been associated with accelerated cardiovascular disease post-transplantation, cholesterol and triglyceride levels warrant close monitoring.

Retinoid	Tablet/capsule strength (mg)	Absorption & Bioavailability		Elimination		
		Peak levels (hr)	Bioavailability (%)	Half-life	Metabolism	Excretion
<i>First-generation retinoids</i>						
Isotretinoin	10, 20, 40	3	25	10-20 hr	Hepatic	Fecal, renal
Tretinoin	10	1-2	-	30-60 min	Hepatic	Fecal, renal
<i>Second-generation retinoids</i>						
Etretinate	10, 25	4	44	80-160 days	Hepatic	Fecal, renal
Acitretin	10, 25	4	60	50 hr	Hepatic	Fecal, renal
<i>Third-generation retinoid</i>						
Bexarotene	75	2	Not known	7 hr	Hepatic	Hepatobiliary

Table 1. Pharmacology of systemic retinoids²⁰

Drug Group	Examples	Effects
Antibiotics		
Rifamycins	Rifampin Rifabutin	Reduction in serum levels of retinoids (via CYP3A4 induction)
Tetracyclines	Doxycycline Minocycline Tetracycline	Risk of pseudotumor cerebri potentially increased
Anticonvulsants		
	Phenytoin	Reduction in serum levels of retinoids (via CYP3A4 induction); may decrease protein binding of phenytoin and increase free fraction
	Phenobarbital	Reduction in serum levels of retinoids (via CYP3A4 induction)
	Carbamazepine	Reduction in serum levels of retinoids (via CYP3A4 induction); possible reduction in carbamazepine efficacy (unknown mechanism)
Immunosuppressive agent	Cyclosporine	Increase in serum levels via competition with retinoids for CYP3A4 metabolism
Hormonal contraceptive	Progestin only “minipill”	Possible reduction in serum levels of minipill, resulting in contraceptive failure
Folate antagonist	Methotrexate	Risk of hepatotoxicity potentially increased
Nutritional	Vitamin A	Hypervitaminosis A-like toxicities
Corticosteroids	Various	Potential for increased risk of bone loss
Habits	Ethanol intake (significant)	Acitretin may “reverse metabolize” to tretinate
Topical acne therapies	Benzoyl peroxide Tretinoin	May increase risk of irritancy

Table 2. Drug interactions with systemic retinoids²⁰

Other known adverse effects include: ocular (i.e., reduced night vision, dry eyes), skeletal (i.e., diffuse skeletal hyperostosis, osteophyte formation, premature epiphyseal closure), gastrointestinal (i.e., nausea, diarrhea, pancreatitis), hepatic (i.e., transaminitis, toxic hepatitis), hematologic (i.e., leukopenia, agranulocytosis), neurologic (i.e., pseudotumor cerebri, depression, suicidal ideation) and muscle (i.e., myalgias, myopathy) involvement.^{10,11,18} Because of the risk of teratogenicity, retinoids are classified as US FDA Pregnancy Category X.

While it has been postulated that retinoids induce immunostimulation, thereby potentiating graft rejection,

these concerns have not been validated.¹⁰ In all studies to date, there have been no significant liver or renal alterations during the treatment or follow-up periods.²³⁻³¹ The potential drug interactions with systemic retinoids and monitoring guidelines are reviewed in Tables 2 and 3.²⁰

Conclusion

Over the years, it has been well recognized that solid organ transplant recipients are at an increased risk of developing skin cancers. Data from a small number of randomized, controlled trials suggest that acitretin may have a beneficial role in high-risk OTRs. While appropriate patient selection (i.e., patients with multiple SCCs) may improve the risk-

Baseline	Follow-up
<ul style="list-style-type: none"> • Serum or urine pregnancy test (in women of childbearing years) • Complete blood count (CBC) • Liver function (AST, ALT, ALP, bilirubin) • Fasting lipid profile (triglycerides, total cholesterol, LDL and HDL cholesterol) • Renal function (blood urea nitrogen, creatinine) 	<ul style="list-style-type: none"> • Monthly for 3 months, then every 3 months • Complete blood count (CBC) • Liver function (AST, ALT) • Fasting lipid profile • Renal function • Serum or urine pregnancy test monthly (in women of childbearing years)

Table 3. Systemic retinoids - laboratory monitoring guidelines²⁰

Abbreviations: AST = aspartate aminotransferase; ALT = alanine transaminase; ALP = alkaline phosphatase; LDL = low-density lipoproteins; HDL = high-density lipoproteins.

benefit ratio, indications for use and optimal dosing regimens have yet to be established.

Given the theoretical risk of allograft rejection with systemic retinoids, low starting doses of acitretin (i.e., 10 mg per day) have been recommended. The dose of acitretin may be increased to 30 mg per day, depending on clinical response and drug tolerability. Since rebound flares occur upon discontinuation of retinoids, chemoprevention should be viewed as a lifelong therapy in OTRs. Further studies are ultimately required to establish the efficacy and long-term safety of systemic retinoids as chemopreventive agents for high-risk transplant recipients.

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Chemotherapy-Induced Hair Loss

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ABSTRACT

Chemotherapy-induced hair loss occurs with an estimated incidence of 65%. Forty-seven percent of female patients consider hair loss to be the most traumatic aspect of chemotherapy and 8% would decline chemotherapy due to fears of hair loss. At present, no approved pharmacologic intervention exists to circumvent this side-effect of anticancer treatment, though a number of agents have been investigated on the basis of the current understanding of the underlying pathobiology. Among the agents that have been evaluated, topical minoxidil was able to reduce the severity or shorten the duration, but it did not prevent hair loss. The major approach to minimize chemotherapy-induced hair loss is by scalp cooling, though most published data on this technique are of poor quality. Fortunately, the condition is usually reversible, and appropriate hair and scalp care along with temporarily wearing a wig may represent the most effective coping strategy. However, some patients may show changes in color and/or texture of regrown hair, and in limited cases the reduction in density may persist.

Key words: chemotherapy, hair loss, scalp cooling, minoxidil, hair care, wig

Chemotherapy-induced hair loss is considered to be one of the most traumatic factors in cancer patient care. Hair loss can negatively impact individual perceptions of appearance, body image, sexuality, and self-esteem, as well as deprive patients of their privacy, because this treatment-related outcome is readily associated with having cancer by the lay public. Forty-seven percent of female cancer patients consider hair loss to be the most traumatic aspect of chemotherapy and 8% would even decline treatment for fear of this impending side-effect.^{1,2}

Incidence of Chemotherapy-Induced Hair Loss

The overall incidence of chemotherapy-induced hair loss is estimated to be 65%.³ The prevalence and severity of this type of hair loss are variable and related to the selected chemotherapeutic agent and treatment protocol. There are multiple classes of anticancer drugs that can induce alopecia

(Table 1), with frequencies of chemotherapy-induced hair loss differing across the four major drug classes: >80% for antimicrotubule agents (e.g., paclitaxel), 60%-100% for topoisomerase inhibitors (e.g., doxorubicin), >60% for alkylators (e.g., cyclophosphamide), and 10%-50% for antimetabolites (e.g., 5-fluorouracil plus leucovorin). Combination therapy consisting of two or more agents usually produces higher incidences of more severe hair loss, when compared with monotherapy.³

Pathobiological Considerations

Chemotherapy-induced hair loss is a consequence of direct toxic insult on the rapidly dividing cells of the hair follicle. While hair loss from anticancer therapy has traditionally been categorized as acute diffuse shedding that is caused by dystrophic anagen effluvium, more recently, it has been highlighted that, in fact, chemotherapy-induced hair loss

Agents that usually cause hair loss	Agents that sometimes cause hair loss	Agents that unusually cause hair loss
Adriamycin	Amsacrine	Carboplatin
Cyclophosphamide	Bleomycin	Capecitabine
Daunorubicin	Busulphan	Carmustine
Docetaxel	Cytarabine	Cisplatin
Epirubicin	5-Fluorouracil	Fludarabine
Etoposide	Gemcitabine	Methotrexate
Ifosfamide	Lomustine	Mitomycin C
Irinotecan	Melphalan	Mitroxantrone
Paclitaxel	Thiotepa	Procarbazine
Topotecan	Vinblastine	Raltritrexate
Vindesine	Vincristine	6-Mercaptopurine
Vinorelbine		Streptozotocin

Table 1. Cytotoxic agents that can cause hair loss³

may present with different pathomechanisms and clinical patterns. Evidence exists suggesting that the hair follicle may respond to the same insult that is capable of stopping mitosis with both shedding patterns, i.e., dystrophic anagen effluvium and telogen effluvium.⁴ Accordingly, the hair may fall out very quickly in clumps or gradually. When mitotic activity is arrested, numerous and interacting factors may influence the shedding pattern. One of these factors is the mitotic activity of the hair follicle at the moment of the insult.

A primary characteristic of the anagen hair follicle is that the epithelial compartment undergoes proliferation, with the bulb matrix cells exhibiting the greatest proliferative activity in building up the hair shaft. The abrupt cessation of mitotic activity leads to weakening of the partially keratinized, proximal portion of the hair shaft, resulting in narrowing and subsequent breakage within the hair canal. The consequence is hair shedding that usually begins at 1 to 3 weeks after initiation of chemotherapy. Due to its long anagen phase, the scalp is the most common location for hair loss, while other terminal hairs are variably affected depending on the percentage of hairs in anagen. Normally, up to 90% of scalp hairs are in the anagen phase, and as such, hair loss is usually copious and results in alopecia that is quite obvious. In addition, chemotherapy given at high doses for a sufficiently long duration and with multiple exposures may also affect hairs of the beard, eyebrows, and eyelashes, as well as axillary and pubic regions.

When hair is in late anagen phase, during which the mitotic rate slows down spontaneously, it simply accelerates its normal path to telogen, while mitotically inactive phases (catagen and telogen) are not affected. Since anagen duration is diminished in androgenetic alopecia, the probability is increased that the antimetabolic insult strikes hairs that are close to the resting phase, resulting in telogen effluvium. Furthermore, synchronization of hair cycles also plays a role, and again in androgenetic alopecia, the hair cycles tend to synchronize due to the shortened duration of anagen. Consequently, even a minor antimetabolic insult can produce marked hair loss.⁵

Generally, the hair loss is reversible, with hair regrowth typically occurring after a delay of 3 to 6 months. In some patients, the new growth shows changes in color and/or texture. Hairs may be curlier than previous or they may be gray until the follicular melanocytes begin functioning again, but these differences are usually temporary.

Permanent alopecia has been reported after chemotherapy with busulfan and cyclophosphamide following bone marrow transplantation,⁶ and it has also been associated with certain risk factors, including chronic graft-versus-host reaction, previous exposure to X-ray, and age of patients.⁷

Therapeutic Potential for Prevention or Reversal of Chemotherapy-Induced Hair Loss

A number of inhibitive measures have been proposed and tried in an effort to limit chemotherapy-induced hair loss. Of the treatments investigated thus far, scalp cooling (hypothermia) has been the most widely used and studied, though most published data on this method are of poor quality. Of the 53 multiple patient studies published between 1973 and 2003 on the results of scalp cooling for the prevention of chemotherapy-induced hair loss, seven⁸⁻¹⁴ of these trials were randomized. In six^{8,9,11-14} of the seven randomized studies, a significant advantage was observed with scalp cooling. The favorable results were most evident when anthracyclines or taxanes were used as the chemotherapeutic agents. Some studies have raised concerns about the risk of scalp skin metastases after cooling.^{15,16} Currently, scalp cooling is contraindicated for those with hematological malignancies and its use is controversial in patients with non-hematological malignancies who undergo curative chemotherapy.¹⁷ Patients undergoing scalp hypothermia commonly report feeling uncomfortably cold and experience headaches.

To date, no approved pharmacologic option exists for the prevention of chemotherapy-induced hair loss. Among the therapies evaluated in cancer patients thus far, the topical hair growth promoting agent minoxidil was able to shorten the duration, but it did not prevent chemotherapy-induced hair loss.¹⁸ Minoxidil also failed to induce significant regrowth of hair in busulfan- and cyclophosphamide-induced permanent alopecia.¹⁹

Advances made in understanding the pathobiology of chemotherapy-induced hair loss, in conjunction with the investigation of several experimental pharmacologic approaches, may offer some optimism. However, the inherent vulnerability rests with the rapid cell proliferation of hair follicle keratinocytes during anagen that renders the structure susceptible to the effects of chemotherapeutic toxicity. A strategy that protects against chemotherapy-induced hair loss may involve arresting the cell cycle in order to reduce the sensitivity of the follicular epithelium to cell cycle-active antitumor agents. Inhibition of cyclin-dependent kinase 2 (CDK2), a positive regulator of the eukaryotic cell cycle, may represent a potential approach that arrests the cell cycle. Potent small-molecule inhibitors of CDK2 are currently being developed using structure-based methods.³ Ultimately, a successful therapeutic candidate should selectively target the hair follicle and avoid interfering with the efficacy of anticancer treatment. In view of the fact that cancer is usually treated with a combination of chemotherapy drugs, an effective mitigation strategy would likely require agents that are effective for different chemotherapeutics with distinct mechanisms of action. Moreover, variations in patient characteristics must also be taken into account, as the pattern of chemotherapy-induced hair loss is patient-specific.

Suggestions for Routine Management

Even if chemotherapy-induced hair loss cannot be prevented, it can be managed. Anticipating hair loss, coming to terms with the inevitability of hair loss, and maintaining a proactive disposition are the key steps in successfully coping with chemotherapy-induced hair loss.

Recommendations for hair care include:²⁰

- Avoiding physical or chemical trauma to the hair (e.g., bleaching, coloring, perming, using curling irons or hot rollers). Implementation of gentle hair care strategies should be continued throughout chemotherapy.
- Using a satin pillowcase, which is less likely to attract and catch fragile hair; using a soft brush, washing hair only as often as necessary; and using a gentle shampoo.
- Cutting hair short or shaving hair. Short hair tends to look fuller than long hair, and when the hair is shed, it is less noticeable when it is short. Moreover, hair that has been cut short may help patients to ease the transition to total alopecia.
- Shaving the head may be easier for securing a wig or hairpiece.

Patients can be encouraged to plan for an appropriate head covering in advance. Clinicians should be mindful that the use of a head covering as the hair falls out is a very personal decision. For women in particular, chemotherapy-induced hair loss involves a confrontation with the very nature of their disease, while for men it is often viewed as a normal and inevitable consequence of treatment. Depending on individual patient preference, temporarily wearing a wig or another type of head covering until the hair regrows may be the most effective way of dealing with this condition, while at the same time this measure can protect the scalp from sun and cold exposure.²¹

Conclusion

The major medical approach to prevent or minimize chemotherapy-induced hair loss remains scalp cooling, while topical minoxidil may speed up hair regrowth. Since chemotherapy-induced hair loss cannot be reliably prevented, it is recommended that a management scheme be devised in advance which focuses on treatment expectations and making patients as comfortable as possible with their appearance before, during, and after anticancer therapy.

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Update on Drugs

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Name/Company	Approval Dates/Comments
Belimumab <i>Benlysta</i> ® Human Genome Sciences/ GlaxoSmithKline	The US FDA and European Medicines Agency (EMA) received a Biologics License Application and Marketing Authorization Application, respectively, in June 2010 for the approval of this human monoclonal antibody for the treatment of systemic lupus erythematosus. Belimumab specifically targets and inhibits the activity of B-lymphocyte stimulator (BLyS®). Elevated levels of BLyS® prolong B cell survival, contributing to autoantibody production. Belimumab reduces autoantibody levels and controls disease activity.
Adapalene 0.1% gel TEVA Pharmaceutical Industries	The US FDA approved a generic version of adapalene 0.1% gel (comparable brand, Differin®, Galderma) in June 2010 for the treatment of acne.
Antiseborrheic compound <i>K301/Kaprolac</i> ® Moberg Derma AB	In April 2010, marketing authorization in the European Union was granted to this novel non-prescription topical solution for the management and relief of scaly and itchy skin associated with common scalp conditions (e.g., seborrheic eczema and dandruff).

Drug News

Ipilimumab (MDX-010 or MDX-101) is a fully human antibody that binds to cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), a molecule on T-cells that plays a central role in immune response regulation. Ipilimumab inhibits the activity of CTLA-4, resulting in sustained antitumor immunity. A phase 3 study* of 676 patients with unresectable stage III or IV melanoma were randomly assigned (3:1:1 ratio) to receive ipilimumab + glycoprotein 100 (gp100) peptide vaccine (403), ipilimumab alone (137), or gp100 alone (136). Ipilimumab, at a dose of 3 mg/kg body weight, was administered with or without gp100 every 3 weeks for up to four treatments. The median overall survival was 10.0 months in patients receiving ipilimumab + gp100, as compared with 6.4 months in patients receiving gp100 alone (hazard ratio [HR] for death, 0.68; p < 0.001). The median overall survival with ipilimumab alone was 10.1 months (HR for death in the comparison with gp100 alone, 0.66; p = 0.003). No difference in overall survival was observed between the ipilimumab groups (HR with ipilimumab + gp100, 1.04; p = 0.76). Grade 3 or 4 immune-related adverse events occurred in 10-15% of patients treated with ipilimumab and in 3% treated with gp100 alone. Both ipilimumab treatment arms demonstrated significant overall survival benefit in patients with metastatic melanoma.

*Hodi FS, et al. *N Engl J Med* (2010 Jun 14) [e-pub ahead of print].

In August 2010, acitretin (Soriatane®, Tribute Pharmaceuticals) will be reintroduced in Canada. Acitretin is a synthetic oral retinoid and is indicated for the treatment of severe psoriasis (including erythrodermic and pustular types) and other keratinizing disorders in patients who are refractory or intolerant to conventional therapies.

In April 2010, eflornithine hydrochloride (HCl) cream 13.9% (Vaniqa®, Triton Pharma Inc.) was re-launched in Canada as the only topical agent indicated for the reduction of unwanted facial hair in women. Eflornithine HCl cream can also be used in combination with laser therapy or in the management of hirsutism.