

Hand foot skin reaction in cancer patients treated with the multikinase inhibitors sorafenib and sunitinib

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Background: This study examined clinicopathological findings and management of hand foot skin reaction (HFSR) to sorafenib and sunitinib in a dermatology referral center for cancer-related toxic effects.

Patients and methods: We identified 12 patients who developed HFSR in a 1-year period (2007). Medical records and histological specimens were investigated for clinicopathological data and results on management.

Results: We identified 12 patients developing HFSR on treatment with sorafenib (83%) or sunitinib (17%). Majority presented with grade 3 (75%) HFSR and a median Skindex score of 43. Biopsies in seven patients showed horizontal layers of keratinocyte necrosis, which correlated to time of drug exposure: early (<30 days from initiation) leading to stratum granulosum–spinosum alterations and late (≥30 days) resulting in stratum corneum pathology. Treatment with topical urea singly ($n = 3$), plus tazarotene ($n = 7$), or fluorouracil ($n = 2$) resulted in ≥2 grade improvement in the majority of patients (58%), with five patients (42%) improving one grade ($P = 0.007$). Median Skindex score at follow-up was 32 ($P = 0.22$).

Conclusions: There are unique clinicopathological characteristics of HFSR due to the multikinase inhibitors that correlate with time of agent initiation. Treatment with topical agents having keratolytic, antiproliferative, and anti-inflammatory properties showed benefit.

Key words: hand foot skin reaction, sorafenib, sunitinib

introduction

Sorafenib and sunitinib are two novel, small molecule multikinase inhibitors (MKIs) that have shown promising results in the inhibition of tumor cell angiogenesis and proliferation [1]. Sorafenib (Nexavar®; Onyx/Bayer Pharmaceuticals, Emoryville, CA and Trenton, NJ) is an oral agent shown to inhibit Raf-1, B-Raf, vascular endothelial growth factor receptor (VEGFR) 2–3, platelet-derived growth factor receptor (PDGFR) β , FLT-3, RET, c-KIT, and p38 α , a member of the MAP kinase family. Sunitinib (Sutent®; Pfizer Inc., New York, NY) is also an oral multitargeted tyrosine kinase inhibitor that targets VEGFR (1–3), PDGFR- α , c-KIT, FLT-3, colony-stimulating factor receptor 1, and the glial cell-line-derived neurotrophic factor receptor [1–3].

Despite their higher specificity when compared with standard chemotherapy, the activity of these agents is not limited to tumor cells. A variety of adverse side-effects have been reported, including diarrhea, hypertension, and nausea. Most notably, cutaneous toxic effects including mucositis (20%), rash (19%–40%), alopecia (27%), xerosis (16%), xerostomia (11%), and hand foot skin reaction (HFSR) (20%–30%) [4–6]. The most clinically significant and dose-limiting dermatologic

toxicity is HFSR, as it may be associated with significant tenderness affecting function and quality of life, which may lead to dose modification or discontinuation of critical antineoplastic therapy [5, 6]. Whereas the severity is low/moderate in the majority of cases, severe (grade 3 per National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE v3.0) HFSR develops in 5%–6% of treated patients, impairing activities of daily living. Phase 1 data have shown increased frequency and severity of HFSR with higher doses of sorafenib, but this has not been observed with sunitinib [7, 8].

In this article, we present the clinicopathological findings of HFSR in seven patients on either sorafenib or sunitinib, and also compare these findings with previously reported findings of hand foot syndrome (HFS) associated with conventional chemotherapeutic agents. In addition, we report results of management of HFSR in 12 patients. Treatment with topical urea, fluorouracil, and tazarotene was on the basis of histological findings of hyperkeratosis, altered differentiation, and inflammation.

materials and methods

patients and samples

The study included 12 patients who were evaluated and treated between January 2007 and November 2007 at the SERIES (Skin and Eye Reactions to Inhibitors of EGFR and kinaseS) Clinic, a dermatology-based clinical and

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research program for the management of skin toxic effects to targeted cancer therapies [9]. Referral was based upon the recognition of HFSR associated with either sorafenib or sunitinib by oncologists. All patients who were biopsied gave their informed consent. Follow-up of patients included a physical examination every 2–4 weeks until resolution or disease progression.

Four-millimeter punch biopsies were obtained from lesional skin in either the hands or the feet of seven patients. The specimens were fixed in formalin, embedded in paraffin, and stained with hematoxylin and eosin. Histological findings were identified and recorded by the study dermatopathologists (JG and PG). Management of HFSR consisted in twice daily application of urea 40% cream in combination with tazarotene 0.1% cream or fluorouracil 5% cream.

grading of HFSR severity and impact on quality of life

Patients received a complete dermatological exam at every visit. Grading of HFSR was carried out using the NCI-CTCAE v3.0 [10]: grade 1 = minimal skin changes or dermatitis (e.g. erythema) without pain, grade 2 = skin changes (e.g. peeling, blisters, bleeding, edema) or pain, not interfering with function, grade 3 = ulcerative dermatitis or skin changes with pain interfering with function. This version was modified from the NCI-Common Toxicity Criteria v2.0; grade 1 = skin changes or dermatitis without pain (e.g. erythema, peeling); grade 2 = skin changes with pain, not interfering with function; grade 3 = skin changes with pain, interfering with function. The dermatology-specific quality-of-life tool Skindex-16 [11] was administered to patients at every visit as part of standard of care in the SERIES Clinic.

statistical analysis

Change in grade was compared between presentation and follow-up using Bowker's test for symmetry [12]. Change in Skindex-16 was compared between presentation and follow-up using the Wilcoxon signed rank test.

results

clinical findings

Demographic and clinical data are summarized in Table 1. The median age of the seven patients was 56.5 years (range 47–83). The associated cancer was renal cell carcinoma in eight cases (66%) and hepatocellular carcinoma for two cases (17%). Development of tender blisters in palms or soles occurred

within 45 days of treatment initiation in all patients (Figure 1). Involvement was bilateral in 8 of 12 patients, and more severe in the soles in 10 of 12 patients. There was no apparent association with hand or foot dominance and severity. Two patients also developed hemorrhagic flaccid bullae on elbows (Figure 2).

Severity of presentation was grade 3 in 75% (9 of 12) of patients and the median Skindex-16 score was 43. Treatment for HFSR was variable (Table 1), with single-agent urea 40% (U) cream twice daily in three patients, tazarotene 0.1% cream (T) plus U in six patients, and 5% fluorouracil cream and U or T in one patient each and one patient on tazarotene 0.1%. Improvement in ≥ 2 grades of severity was observed in seven patients, with five patients improving one grade in severity. There was significant improvement between presentation and follow-up in that all patients improved ($P = 0.007$). No patients showed worsening or stable disease at follow-up. Median Skindex-16 score at follow-up was 32 ($P = 0.22$, compared with median score of 43 at presentation).

histological findings

Histological findings of lesional palmoplantar skin are summarized in Table 2. A total of seven biopsies were taken. Epidermal alterations were characterized by band-like areas of necrotic keratinocytes in all patients, two of which were associated with blistering (Figure 1). The level of keratinocyte necrosis varied, with 2 patients showing abnormalities in the stratum spinosum–granulosum (biopsies obtained at days 12 and 19), which were manifest by horizontal layers of keratinocyte necrosis and discohesiveness (Figure 3). In the other five patients, abnormalities in the stratum corneum (SC) (biopsies obtained at ≥ 30 days from MKI initiation) were characterized by hyperkeratosis and a layer of parakeratosis (Figure 3).

All biopsies revealed some superficial telangiectasias and a mild perivascular lymphohistiocytic infiltrate. The infiltrate was notable for the absence of eosinophils or neutrophils. Subtle abnormalities of the sweat glands consisting of dilation with dysmorphic eccrine cells, having scant cytoplasm and

Table 1. Patient demographics and results of intervention

Patient/tumor/agent-dose	Age/sex/race	Grade at presentation	Skindex-16 at presentation	Management	Grade at follow-up	Skindex-16 at follow-up
1/HCC/sorafenib 400 mg b.i.d.	71/M/A	3	75	Tazarotene 0.1%/urea 40%	1	46
2/RCC/sorafenib 400 mg b.i.d.	72/M/C	3	73	Urea 40%	2	55
3/HCC/sorafenib 200 mg b.i.d.	50/F/AA	3	24	Tazarotene 0.1%/urea 40%	1	21
4/RCC/sorafenib 400 mg b.i.d.	54/M/C	3	26	Urea 40%/5% fluorouracil	1	11
5/RCC/sunitinib 50 mg everyday	55/M/C	3	N/A	Tazarotene 0.1%/urea 40%	1	N/A
6/RCC/sunitinib 50 mg q.d.	59/M/C	3	N/A	Urea 40%	1	N/A
7/RCC/sorafenib 200 mg b.i.d.	50/M/A	2	43	Tazarotene 0.1%/urea 40%	1	27
8/HCC/sorafenib 400 mg b.i.d.	59/F/C	2	56	Tazarotene 0.1%	1	32
9/BVT/sorafenib 400 mg b.i.d.	49/F/C	2	N/A	Urea 40%	1	N/A
10/RCC/sorafenib 400 mg b.i.d.	47/F/C	3	N/A	Tazarotene 0.1%/urea 40%	1	N/A
11/ovarian/sorafenib 400 mg b.i.d.	58/F/C	3	14	Tazarotene 0.1%/urea 40%	2	41
12/RCC/sorafenib 400 mg b.i.d.	83/F/H	3	N/A	Tazarotene 0.1%/5% fluorouracil	1	N/A

RCC, renal cell carcinoma; HCC, hepatocellular carcinoma; BVT, blood vessel tumor; Ovarian, ovarian carcinoma. AA, African American; A, Asian; C, Caucasian; H, Hispanic; N/A, not available; M, male; F, female.



Figure 1. Clinical presentation of hand foot skin reaction. Early involvement of the palms (left upper panel, patient 1) and soles (right upper panel, patient 9). Late clinical presentation involving the palms (left lower panel, patient 7) and soles (right lower panel, patient 7).



Figure 2. Flaccid bullae and erosions on elbows, presenting simultaneously to hand foot skin reaction, as seen in patient 2.

cystic changes were seen in five patients (all of which had biopsies at day ≥ 30 from MKI initiation) (Figure 4).

discussion

This study describes clinical, histological, and management characteristics of HFSR in 12 patients treated with the MKIs sorafenib and sunitinib. We found that HFSR manifests with tender palmoplantar lesions especially in areas of trauma or

friction (Figure 1), leading to significant alterations in quality of life (median Skindex score = 43). Histologically, alterations in keratinocytes included parakeratosis and apoptosis, along with telangiectasias and a mild inflammatory infiltrate. The level of keratinocyte alteration correlated with the time of exposure to MKI patients initiating therapy < 30 days showed abnormalities at lower levels of the epidermis (e.g. stratum spinosum–granulosum), when compared with patients treated for ≥ 30 days (alterations in the SC) (Figure 3). Some cases demonstrated alterations in eccrine glands (Figure 4). The consistent appearance of this reaction in patients treated with MKIs (20%–30%), along with similar histological findings described in this article, indicates a mechanism-based effect.

The spectrum of inhibition for sorafenib and sunitinib overlaps in VEGFR, PDGFR, c-KIT, and FLT-3 [4], which indicates that inhibition of one or a combination of these receptors/pathways plays a role in HFSR development. It is unlikely that PDGFR inhibition alone accounts for this effect, as the PDGFR-targeting agent imatinib does not result in high rates of HFSR [13]. Similarly, small molecules or monoclonal antibodies specifically blocking the VEGFR do not lead to HFSR [14]. It is noteworthy that the addition of the anti-VEGF antibody bevacizumab to erlotinib and imatinib did not result in HFSR [15]. This may be due to differences in pathway inhibition or the inability of bevacizumab to effectively block VEGFR signaling in skin, which is highlighted by the infrequent development of cutaneous toxic effects in patients treated with this agent.

Obligate interactions between the epidermis and dermis for cutaneous maintenance and regeneration [16] indicate that alterations in either component may lead to a cascade of pathological events, as seen in HFSR. Long-term skin equivalents show that keratinocytes and fibroblasts are mutually dependent for proliferation, migration, differentiation, and formation of the basement membrane zone [17]. Whereas keratinocytes do not express PDGFR or VEGFR, all isoforms of PDGF (A and B chains) are synthesized in normal and wounded human skin by keratinocytes [18]. On the other hand, dermal fibroblasts and endothelial cells express PDGF-specific cell surface receptors which allow for autocrine or paracrine activation [19]. As sorafenib and sunitinib both target VEGFR, PDGFR, and c-KIT, the capillary endothelium may be the first target in HFSR, as these agents have been shown to enhance tumor vessel regression via inhibition of endothelial cell survival [20] and the observation that adding bevacizumab to sorafenib appears to result in greater toxicity [21]. Such an effect, which is localized and magnified in areas of trauma or friction (e.g. palms, soles, elbows) where affected vessels and fibroblasts are unable to repair after daily use, would lead to inflammation. Another factor which may explain the localization in the palmoplantar surfaces is the high density of c-KIT and PDGF-R bearing eccrine [22, 23] glands at these sites. On the other hand, RET and FLT-3 have not been demonstrated in cutaneous structures. All the deleterious events in the dermis could lead to epidermal damage through decreased release of survival factors, with subsequent keratinocyte apoptosis, release of inflammatory chemokines with ensuing clinical symptoms. Animal models which demonstrate dermatologic features reminiscent of patients

Table 2. Summary of histological findings

Patient	Site of biopsy	Day of biopsy from MKI initiation	Level of keratinocyte alteration	Necrotic cells	Hyperkeratosis	Telangiectasia	Abnormality of sweat gland
1	Right hand	12	Intraepidermal	+	–	P	–
2	Right heel	19	Intraepidermal	+	–	P	–
3	Left hand	30	Lower SC	+	+	P	+
4	Left hand	30	Lower SC	+	+	S	+
5	Left heel	45	Upper SC	–	+	S	+
6	Right heel	45	Upper SC	–	+	S	+
7	Right heel	150	SC	–	+	S	+

(+), present; (–), absent; S, slight; P, prominent; MKI, multikinase inhibitor sorafenib or sunitinib; SC, stratum corneum.

treated with MKIs include mice engineered with deficient PDGF signaling. PDGFR- α knockout mice will develop subepidermal blebs [24], whereas PDGFR- β [25] and PDGF-C [26] deficient animals will show purpuric lesions which histologically consist of subcutaneous accumulation of erythrocytes and severe subepidermal blistering, respectively.

In contrast to HFS to conventional cytotoxic agents [27, 28–31] in which clinical signs consist of symmetrical erythema and edema in the palms and soles, which may evolve into necrosis and blistering desquamation, followed by ulceration and crusting, the patients treated with MKIs presented in this article developed localized, tender lesions, which appeared as blisters or hyperkeratosis, which in some cases were surrounded by an erythematous halo. These lesions were almost always localized to areas of friction or trauma, such as over the interphalangeal joints, distal phalanges, or heels. With conventional antineoplastic agents it has also been hypothesized that elimination via eccrine glands results in the toxicity on areas where they are in highest density—the palms and soles [32]. In addition, there is some evidence that rupture of capillaries associated with activity, causes extravasation of the drug leading to an inflammatory reaction [33]. Sweat glands may also be a target of MKIs, as PDGF and c-KIT are both expressed in sweat duct epithelium, and eccrine squamous syringometaplasia has been described with sunitinib [34] and imatinib [35]. Vessel ectasia was also observed in all our patients indicating these structures as potential targets.

Consistent histologic findings [28, 29] in HFS induced by capecitabine and pegylated doxorubicin include focal vacuolization and pyknosis in the basal cell layer, spongiosis, and hyperkeratosis with parakeratosis. Ectatic blood vessels and a mild perivascular lymphohistiocytic infiltrate are also apparent in the dermis. Whereas most reports revealed no significant pathology of the eccrine glands, a few case reports indicated sweat gland abnormalities, including eccrine squamous syringometaplasia and a perieccrine and eccrine inflammatory infiltrate. Docetaxel HFS has led to epidermal dysmaturation, a perivascular infiltrate with neutrophils and squamous syringometaplasia [30]. A study of 12 biopsies of patients treated with multiple agents including fluorouracil, doxorubicin, vinorelbine, methotrexate, cytarabine, and cyclophosphamide [31] showed histological changes that correlated with clinical severity: grade 1 HFS showing capillary dilation and basal cell abnormalities; grade 2 demonstrated

capillary dilation with papillary dermal edema, and interphase dermatitis, basal layer degeneration, and scattered necrotic keratinocytes; HFS grade 3 revealed abundant necrotic keratinocytes, edema, epidermal separation, and interphase dermatitis [29].

Histological analysis of seven biopsies in our patients consistently showed necrotic keratinocytes, telangiectasias, and a mild perivascular lymphohistiocytic infiltrate. In the epidermis, a well-defined horizontal zone of keratinocyte necrosis and discohesis was observed at different layers depending on time of exposure to drug: if the MKI had been initiated earlier than 30 days (patients 1–2), it was intraepidermal, whereas longer exposure times (≥ 30 days) yielded alterations in various levels of the outermost SC (patients 3–7). The SC was intact in < 30 day MKI-exposed patients and always involved in those exposed ≥ 30 days, in which the necrotic keratinocytes appeared as a layer of parakeratosis. The horizontal area of necrotic keratinocytes was distinct from the basal vacuolization or scattered pyknotic cells seen with anthracyclines [29]. Alterations in the SC were hallmarked by parakeratosis and hyperkeratosis which appeared clinically as an acquired palmoplantar keratoderma (PPK). A similar observation has been described in two patients developing HFS to capecitabine, suggesting that SC alterations and PPK are a sequential event after HFS [36] or HFSR [37]. In addition to keratinocyte necrosis, other reports of HFSR to MKIs describe lesions with parakeratosis and hyperkeratosis, along with dermal edema and an infiltrate with neutrophils and eosinophils [37–39]. These patients differ from our observations in that ≤ 30 days had elapsed since drug initiation and SC alterations were visible and many eosinophils and neutrophils were present in the dermis. However, these reports are consistent with our findings of dyskeratinocytes, confluent keratinocyte necrosis, and intraepidermal separation. Necrotic keratinocytes were observed in our series of patients only in those who were treated with the MKI for ≤ 30 days, suggesting that longer treatment leads to adaptive mechanisms in the epidermis which minimize keratinocyte demise.

On the basis of the histological findings of hyperkeratosis, keratinocyte necrosis, and dermal inflammation observed in our patients with HFSR, it was decided to treat with urea, tazarotene, or fluorouracil. Urea is a keratolytic that dissolves the intercellular matrix, which results in loosening the horny layer of skin and the shedding of scaly skin, thereby softening

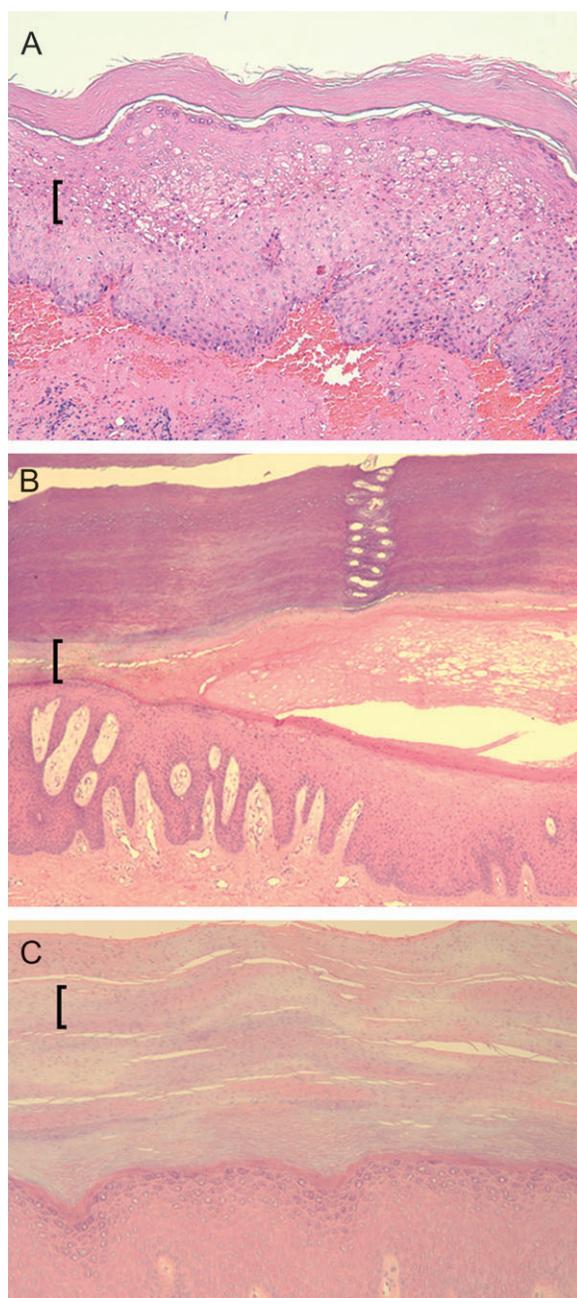


Figure 3. Effect of time of multikinase inhibitor exposure to level of keratinocyte necrosis within the epidermis. (A) Biopsy at day 12 reveals involvement at the stratum spinosum; (B) lower stratum corneum affected at day 30; (C) upper stratum corneum at day 45. Brackets, necrotic keratinocytes.

hyperkeratotic areas, effectively reducing epidermal thickness and proliferation [40]. Tazarotene decreases epidermal proliferation, normalizes differentiation, and reduces dermal inflammation, all of which have led to the approval of this agent in psoriasis [41]. Although systemic administration of the antifolate fluorouracil and its prodrug capecitabine have been associated with HFS in 18% and 0.6% of patients [42], respectively, its topical application has shown anecdotal benefit in the treatment of inherited dermatologic conditions

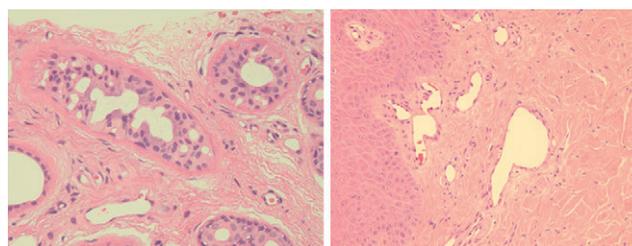


Figure 4. Histological alterations in the dermis of hand foot skin reaction lesions included cystic degeneration of eccrine glands (left panel) and telangiectasias (right panel).

characterized by tender hyperkeratotic palmoplantar lesions, likely via its antiproliferative effect on keratinocytes [43, 44]. In six of seven patients, urea 40% cream applied twice daily as single agent ($n = 2$) and in combination with tazarotene 0.1% cream ($n = 3$) or fluorouracil 5% cream ($n = 1$) resulted in one grade improvement in severity in two patients and two grades in four patients. Overall, significant improvement between presentation and follow-up was evidenced in every patient ($P = 0.007$). With the exception of one patient that did improve objectively, those who completed the Skindex-16, showed an improvement in dermatologic-related quality of life.

Although the current study is limited by its uncontrolled nature, it raises important questions regarding HFSR management. First, that histological findings can yield clues towards the use of tailored agents against the toxicity. Since cancer patients are usually on multiple medicines and have significant comorbidities, it is critical that antitoxicity interventions are devoid of significant side-effects. Therefore, topical agents such as the ones evaluated in this article represent a viable alternative. Second, the use of quality-of-life tools is desirable in supportive care studies. In our study, not only did the Skindex-16 correlate with clinical improvement but it also evidenced an improvement that enabled patients to endure the toxicity while receiving anticancer therapy. Lastly, anti-HFSR interventions should not only be limited to treating an established but rather focus on prevention, as once keratinocyte death occurs, treatment is limited to a damage control exercise.

The management of HFSR is considered a priority in patient care as well as research endeavors with MKIs. There are currently no published randomized clinical trials for the management of this untoward event. For HFS induced by cytotoxic agents, uncontrolled data have shown benefit with the use of topical dimethyl sulfoxide, Bag Balm®, oral dexamethasone, celecoxib, and pyridoxine [27]. Treatment of HFSR to MKIs with moisturizers, shock absorbers, corticosteroids, urea has been recommended by other authors [45–47]. On the basis of histological observations, we were able to rationally use agents shown to counter the clinical and histological events induced by MKIs (i.e. urea, fluorouracil, and tazarotene). Moreover, the histological observation of well-demarcated zones of keratinocyte necrosis and anecdotal reports of HFSR resolution with continued MKI therapy indicate that dose-escalation studies are warranted. Further evaluation of these agents in the

randomized setting is critical for the optimization of therapies with MKIs as well as maintenance of quality of life.

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