Inflamed actinic keratoses as a biomarker in repositioning of chemotherapeutics: a systematic review and meta-analysis

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ABSTRACT

Background: Inflammation of actinic keratoses (AK) was originally described with systemic 5-fluorouracil, and led to the development of topical fluorouracil. Similar observations using different chemotherapeutics may point to other drugs with a potential for repositioning.

Objective: This systematic review aims to evaluate chemotherapeutic agents linked to inflammation-induced cure of AK.

Methods: This systematic review was registered in PROSPERO (CRD42022346168) and followed PRISMA guidelines. A comprehensive literature search for eligible original articles written in English and published in peer-reviewed journals until July 13, 2022 was conducted in MEDLINE and Embase.

Results: 28 articles met inclusion criteria accounting for 36 patients (mean age 68.4 ± 8.3 years) with inflamed AK, exposed to 21 different chemotherapeutic agents – 21/36 (58.3%) received monotherapy and 15/36 (41.7%) received multidrug combinations. Regression was complete in 13/28 (46.4%) and partial in 14/28 (50.0%) of inflamed AK. Cure rates of inflamed AK in multidrug combinations were not superior to monotherapies (p = .252), leading to the observation that the majority of the former (14/15; 93.3%) encompassed one of five chemotherapeutic agents linked to AK inflammation also as a monotherapy.

Conclusion: Overall, inflammation partially/completely cured AK in 96.4% of patients (27/28). Taxanes, pemetrexed, and doxorubicin might have the potential for the management of AK.

Introduction

Each year approximately 19 million patients are diagnosed with cancer worldwide and a substantial proportion subsequently undergoes chemotherapy (1). Despite their therapeutic advantages, chemotherapeutic agents can cause a broad spectrum of mucocutaneous adverse effects, some of which may even lead to the discovery of new treatments. Inflammation of manifested and/or subclinical actinic keratoses (AK) may suggest a meaningful effect of the drug for this new indication. Such serendipities were originally described with systemic 5-fluorouracil (FU) and led to the development of topical FU, a product registered for the management of AK (2,3). Similar observations have been made for other chemotherapeutics without the ensuing development.

Information about inflamed AK following systemic chemotherapy with other agents is scant (4). The aim of this publication is to provide the data in the form of a systematic review of this in order to encourage research into underlying pathophysiological mechanisms, potentially leading to the introduction of new therapies for AK.

Materials and methods

This systematic review was registered in PROSPERO (registration number CRD42022346168) and was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (5). A comprehensive literature search for eligible manuscripts was conducted in the MEDLINE and Embase databases through Ovid on July 13, 2022 using the following terms: actinic keratoses; inflammation; inflamed; anti-neoplastic agents; chemotherapy; chemotherapeutic; cancer; neoplasm. A full search strategy for MEDLINE can be found under Supplement Material 1. Additional articles were identified by hand searching references of all relevant manuscripts. An article was included if it was written in English, published in a peer-reviewed journal, was original, and presented patients with inflammation of AK following chemotherapy, currently authorized for use by European Medicines Agency. The date of publication was not restricted. Articles without specific mention of inflammation when describing the occurrence of AK during chemotherapy were excluded from this review. After duplicate removal, two reviewers (SSB, IP) independently evaluated titles and/or abstracts of the retrieved records. Additionally, articles were excluded based on the full-text evaluation. In cases of discrepancy between the two reviewers, a consensus was reached with the help of the third author (GBEJ). From each included publication, data about publication information, patients’ demographic data, chemotherapeutics used, clinical findings, diagnostic procedures, times of onset of inflammation of AK, and their outcomes (predefined as ‘unchanged,’ ‘partial,’ and ‘complete’
regression/cure of AK) with times of outcome evaluation and management of inflamed AK were extracted independently by two authors (SSB, IP) using Excel Sheet. The risk of bias in analytical studies was assessed using the Newcastle–Ottawa Scale (6). The cut-off value for inclusion was set at a score of ≤3 stars. Quality of evidence was rated as suggested by the GRADE working group (7). Statistical analysis was performed with SPSS software (version 28.0.0.0, IBM, Chicago, IL). Categorical variables were compared using Fischer’s Exact Test, while Kruskal–Wallis Test was used to compare the significance of association between categorical and numeric variables that were not normally distributed. A p-value less than .05 was considered statistically significant.

**Results**

The PRISMA checklist of this systematic review is provided as Supplement Material 2. The search of MEDLINE and Embase provided a total of 2004 citations. After excluding duplicates (n = 143), additional articles were excluded based on title/abstract (n = 1797) and if necessary on full text (n = 40). With the addition of four articles identified by searching the references of relevant papers, a total of 28 articles (26 case reports and 2 case series) involving 36 patients met our inclusion criteria (8–35). The whole selection process is summarized in a PRISMA flow diagram in Figure 1.

The mean age of the patients was 68.4 ± 8.3 years. The female–male ratio was 1:1. 17/23 (73.9%) patients had known AK before initiation of chemotherapy. In total, 21 different chemotherapeutic agents were prescribed to the patients. Monotherapy was carried out in 21/36 (58.3%) patients with 11 different chemotherapeutics: capecitabine (8/21; 38.1%), 5-FU (4/21; 19.0%), while others were prescribed only in one patient each, including sorafenib, sunitinib, erlotinib, docetaxel, paclitaxel, pemetrexed, pentostatin, panitumumab, and doxorubicin. Table 1 presents the pharmacodynamic properties of chemotherapeutic agents used as a monotherapy, basic demographic data of treated patients, time of onset of AK inflammation as well as outcomes of inflamed AK with estimated times of evaluation of the latter.

The second group of patients (15/36; 41.7%) received combinations of chemotherapeutic agents: 6/15 (40.0%) patients 5-FU and cisplatin, while other combinations were prescribed in only one patient each. Table 2 presents data about multidrug combinations, patients’ demographic data, time of onset of AK inflammation, and outcomes of inflamed AK with estimated times of evaluation of the latter.

The overall median time from initiation of chemotherapeutic agents to AK inflammation was 10.0 days (95% CI [8.1, 15.8]) and was not significantly different between subgroups of chemotherapy (5-FU, capecitabine, other monotherapies, 5-FU in multidrug combinations, multidrug combinations without 5-FU) (H = 6.032; p = .197) as can be seen in Table 3, which also shows median times of outcome evaluation and outcomes/cure rates of inflamed AK.

All lesions were located on photo-exposed sites and their features were characteristic of inflamed AK (35/36; 97.2%) except in one patient in whom dark red macules, purpuric papules, and hemorrhagic vesicles were observed (41). Lesions were pruritic (16/24; 66.6%), painful (3/24; 12.5%), burning (1/24; 4.2%) or all three at once (1/24; 4.2%). Three (12.5%) patients were asymptomatic. The diagnosis of inflamed AK was solely clinical in half of the cases (18/36; 50.0%). The other half of the patients (18/36; 50.0%) underwent a biopsy with the histopathological examination, which showed characteristic AK and in a proportion of samples (14/18; 77.8%) additionally various inflammatory infiltrates: (band-like) lymphocytic, lymphohistiocytic, mixed or unspecified. The median time of outcome evaluation

**Figure 1.** Flow diagram of literature search and article selection.
| Chemotherapeutic group | Chemotherapeutic agents (reference) | Targets | Mechanism of action | Indications by EMA in oncology | Patient’s age/gender (reference) | Time of onset of inflamed AK (days after starting chemotherapy) | Time of outcome evaluation of inflamed AK (weeks)/outcome of inflamed AK (unchanged AK, partial or complete regression/cure of AK) |
|------------------------|-------------------------------------|---------|---------------------|-----------------------------|-------------------------------|---------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Protein kinase inhibitors (multikinase inhibitors) | Sorafenib (8) | CRAF, BRAF, VEGFR, PDGFR-R, FLT-3, c-KIT | Anti-proliferative and anti-angiogenic properties | Hepatomsllar, renal cell and differentiated thyroid carcinoma | 63/M (9) | Within weeks | NA/NA |
|            | Sunitinib (10) | PDGFR, VEGFR, KIT, FLT3, CSF-1R, RET | Inhibition of cell proliferation and inducing apoptosis of the cells | GIST, pNET, renal carcinoma | 73/M (11) | 28 | 8/complete |
|            | Erlotinib (12) | EGFR | NSCLC and pancreatic cancer | 77/M (13) | 10 | 8/unchanged |
| Taxanes | Docetaxel (14) | Tubulin | Anti-mitotic properties by stabilizing microtubular network | Breast, prostate, head and neck cancer, NSCLC and gastric adenocarcinoma | 81/M (15) | Rapidly after first infusion | 3/partial |
|            | Paclitaxel (16) | | | Breast cancer, pancreatic adenocarcinoma, NSCLC | 56/F (17) | 42 | NA/NA |
| Folic acid analogues (antifolate agents) | Pemetrexed (18) | TS, DHFR, GARFT | Inhibition of cell replication by disrupting crucial folate-dependent metabolic processes | Malignant pleural mesothelioma, NSCLC | 81/M (19) | 10 | 8/partial |
| Pyrimidine analogues | Capecitabine (precursor of 5-FU) (20) | TS | Provokes unbalanced growth and death of cells by inhibition of DNA, RNA and protein synthesis | Colon, colorectal, gastric, breast cancer | 84/F (21) | 12 | Several days after stopping CT/partial |
|            | | | | 72/F (22) | 7 | 1 month after stopping CT/partial |
|            | | | | 65/M (23) | After the 2nd cycle | NA/complete |
|            | | | | 78/F (24) | 10 | 4,5/complete |
|            | | | | 56/F (25) | 14 | 3/partial |
|            | | | | 69/F (26) | 10 | NA/NA |
|            | | | | 67/M (27) | 4 | 8/partial |
|            | | | | 65/M (28) | After the 1st cycle | NA/NA |
|            | | | | 67/F (29) | 8 | 1/partial |
|            | | | | 72/F (30) | 28 | 8/complete |
|            | | | | 67/F (31) | 7 | 4/partial |
|            | | | | 65/M (32) | After stopping CT/partial | |
| Monoclonal antibodies | Panitumumab (34) | EGFR | Binding results in inhibition of cell growth, induction of apoptosis and decreasing of IL-8 and VEGF | Colorectal cancer | 80/F (35) | NA | NA/NA |
| Anthracyclines and related substances | Doxorubicin (36) | DNA-bases | Cytotoxic effects by inhibition of DNA, RNA and protein synthesis | Breast, ovarian cancer, multiple myeloma, Kaposi sarcoma | 67/F (37) | NA | 2/partial |
| Purine analogues | Pentostatin (2'-deoxycoformycin) (37) | ADA | Inhibits ADA, RNA synthesis and increases DNA damage | Hairy cell leukemia | 70/M (38) | 28 | After stopping CT/partial |

ADA: adenosine deaminase; AK: actinic keratoses; ALL: acute lymphoblastic leukemia; BRAF: serine-threonine kinase; c-KIT: receptor tyrosine kinase; CRAF: serin/threonine-protein kinase; CSF-1R: colony-stimulating factor receptor; DHFR: dihydrofolate reductase; DNA: deoxyribonucleic acid; EGFR: epidermal growth factor receptor; EMA: European Medicines Agency; F: female; FLT3: Fms-like tyrosine kinase-3; GARFT: glycinamide ribonucleotide formyltransferase; GIST: gastrointestinal stromal tumor; IL: interleukin; KIT: stem cell factor receptor; M: male; NA: not available; NSCLC: non-small cell lung cancer; PDGFR: platelet-derived growth factor receptors; pNET: pancreatic neuroendocrine tumors; RET: glial cell-line derived neurotrophic factor receptor; RNA: ribonucleic acid; SCLC: small cell lung cancer; TS: thymidylate synthase; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptors.
Table 2. Multidrug combinations of chemotherapeutic agents associated with inflammation of actinic keratoses.

| Chemotherapeutic agents | Patient’s age/gender (reference) | Time of onset of inflamed AK (days after starting chemotherapy) | Time of outcome evaluation of inflamed AK (weeks)/outcome of inflamed AK (unchanged AK, partial or complete regression/cure of AK) |
|-------------------------|----------------------------------|---------------------------------------------------------------|---------------------------------------------------------------------|
| Carboplatin, pemetrexed  | 68/F (39)                        | referred 13                                                  | NA/NA                                                               |
| Carboplatin, docetaxel   | 54/M (40)                        | 6 days after 2nd cycle                                       | NA/partial                                                         |
| Carboplatin, paclitaxel  | 67/M (41)                        | 14                                                          | NA/NA                                                               |
| Doxorubicin, cyclophosphamide | 61/F (42)                  | 14                                                          | After stopping CT/partial                                           |
| Doxorubicin, cyclophosphamide, vincristine, rituximab | 68/M (43) | NA | After stopping CT/complete |
| Doxorubicin, vincristine  | 75/F (33)                        | 1 week after initiating therapy 3 complete                  |                                                                     |
| Dactinomycin, vincristine, dacarbazine | 44/M (33) | 4 | 3 complete |
| S-fluorouracil, cisplatin | 73/M (33)                        | 6                                                          | 2/complete                                                         |
|                         | 74/F (33)                        | 2                                                          | NA/NA                                                               |
|                         | 69/F (33)                        | 4                                                          | 1/complete                                                         |
|                         | 64/M (44)                        | Day 5 of the 2nd cycle                                       | Quick/complete                                                     |
|                         | 66/M (31)                        | 21                                                         | Several weeks later/partial                                        |
|                         | 67/F (31)                        | 14                                                         | NA/partial                                                         |
| S-fluorouracil, leucovorin, interferon alpha | 64/M (45) | 4 | After stopping CT/complete |
| S-fluorouracil, cyclophosphamide, methotrexate | 53/F (46) | 0.5 | 2/complete |

AK: actinic keratoses; CT: chemotherapy; F: female; NA: not available; M: male.

Table 3. Comparison of subgroups of chemotherapeutics according to outcomes of inflamed AK, median times from chemotherapy initiation to inflammation of actinic keratoses and median times of outcome evaluation of inflamed actinic keratoses.

| Variables                                | S-FU (n = 4) | Capcitabine (n = 8) | S-FU in multidrug combinations (n = 9) | Other chemotherapeutics prescribed as monotherapy (n = 7) | Multidrug combinations without S-FU (n = 7) | p-Value |
|------------------------------------------|--------------|---------------------|----------------------------------------|----------------------------------------------------------|---------------------------------------------|---------|
| Outcome of inflamed AK                  |              |                     |                                        |                                                          |                                             | .583    |
| Unchanged AK                             | 0/0%         | 0/0%                | 0/0%                                   | 1/6; 16.7%                                               | 0/0%                                        | .583    |
| Complete regression/cure of AK           | 2/4; 50.0%   | 3/6; 50.0%          | 2/7; 28.6%                             | 4/6; 66.7%                                               | 2/5; 40.0%                                  |         |
| Median time of initiation of chemotherapy | 7.5          | 10.0                | 4.0                                    | 19.0                                                     | 10.5                                        | .197    |
| Median time of outcome evaluation of inflamed AK (weeks) | 4.0          | 4.5                 | 2.0                                    | 2.5                                                      | 3.0                                         | .504    |

AK: actinic keratoses; FU: fluorouracil; NA: not available.

Discussion
Systemic chemotherapy can induce inflammatory reactions of AK. Of the inflamed AK, 27/28 (96.4%) cases regressed partially or completely (11,15,21–25,27,30–33,38,40,42–47). These high cure rates imply the opportunity for repositioning more drugs for the treatment of AK, the development of which stems from simple but careful monitoring of the patients. Successful registration of topical FU for the management of AK is an example. In 1962 Falkson and Schulz observed the inflammation of AK during chemotherapy and linked it to S-FU treatment (2). Our systematic review identified additional 20 chemotherapeutic agents, possibly connected to a similar reaction. By observing that 20/36 (55.6%) of all enrolled patients were exposed to S-FU or its prodrug capcitabine, we confirmed the previous findings of their association with AK inflammation (48,49). From this, we can hypothesize that the observation of their link with inflammation and the subsequent regression of AK is also valid for the remaining chemotherapeutic agents. Due to the small number of reported cases, we could not analyze them in detail. However, in order to compare times of inflamed AK occurrence, times of outcome evaluation, and cure rates of inflamed AK, we divided chemotherapeutic agents into meaningful groups of chemotherapeutics into meaningful subgroups of chemotherapeutics (H = 3.699; p = .448). Inflamed AK partially or completely regressed in 46.4% (13/28) and 50.0% (14/28) of patients, respectively. Only in one patient (3.6%) were AK at outcome evaluation unchanged. Outcome data of inflamed AK were not available for 8 patients. The outcomes of inflamed AK did not differ significantly between different subgroups of chemotherapeutic agents (χ² = 6.825; p = .583) and there was no significant difference, either when we compared monotherapies (16/28; 57.1%) with multidrug combinations of chemotherapeutics (12/28; 42.9%) (χ² = 2.692; p = .252). Moreover, the outcome of inflamed AK also did not differ between patients in whom chemotherapy was adjusted in any way (i.e., discontinued, dose reduced, the next cycle delayed) after inflamed AK had been observed (17/30; 56.7%) and patients who continued chemotherapy as previously intended (13/30; 43.3%) (χ² = 1.733; p = .524). The majority of inflamed AK (21/27; 77.8%) required treatment (topical corticosteroids, systemic corticosteroids, topical antibiotics, antihistamines, topical anesthetics, imiquimod, and/or analgesics), which, however, did not influence their outcome (χ² = 4.866; p = .098).
pharmacological groups: 5-FU (4/36) (22–25), capecitabine (8/36) (21–28), other monotherapies (9/36) (9,11,13,15,17,33,35,38,47), 5-FU in multidrug combinations (8/36) (31,33,44–46) and multidrug combinations without 5-FU (7/36) (33,39–43). Although we expected at least a higher cure rate of AK with any of the two multidrug combinations, none of the mentioned variables differed significantly between the groups. The hypothesis of a potentiated effect of multidrug combinations on cure rates of AK was once again disproved when we, with the desire to increase statistical power, compared all monotherapies with all multidrug combinations of chemotherapeutics. This leads to thinking about whether only certain chemotherapy agents provoke inflammation-induced cure of AK and are thus suitable for future development of topical products. Careful observation of all 15 multidrug combinations of chemotherapeutics included in this systematic review showed that the majority of them (14/15; 93.3%) encompassed one of five chemotherapeutic agents linked to AK inflammation also as a monotherapy (31,33,39–46). Excluding 5-FU, docetaxel, paclitaxel, pemetrexed, and doxorubicin might thus have higher potential for the management of AK, narrowing down the candidates for the development of topical products. We have reviewed their possible underlying pharmacodynamic properties. In order to cure AK, drugs have to act against clonal expansions of keratinocytes, caused by ultraviolet-induced mutations of deoxyribonucleic acid (DNA) and subsequent suppression of the tumor suppressor protein p53 (19). Topical FU by mimicking 5-thymine prevents its utilization in DNA and ribonucleic acid synthesis, which provokes the death of cells and inhibits their growth (3). Docetaxel and paclitaxel both belong to the pharmacological groups of taxanes, while pemetrexed and doxorubicin are classified among antifolate agents and anthracyclines, respectively. As cytostatics, they act by the following mechanisms: stabilization of microtubular network, disruption of crucial folate-dependent metabolic processes, and intercalation between adjacent base pairs of the DNA helix to prevent their unwinding for replication (14,16,18,36).

However, more research is needed to measure the number needed to treat to encounter this additional outcome of interest. Only one retrospective and one prospective study investigated the frequency of chemotherapy-induced inflammation of AK but none of them provided data regarding the rate of subsequent regression of AK. The former recorded AK inflammation in 2/138 (1.5%), while the latter recorded it in 3.2% of 128 patients receiving various chemotherapy agents (calculated from a bar chart using Plot Digitizer software) (50,51).

To sum up, additional research is warranted to properly identify chemotherapeutic agents with the highest and most frequent cure rates of AK. The authors thus suggest that future prospective studies on adverse effects that occur during chemotherapy also observe the phenomenon of inflamed AK with long enough monitoring to be able to assess whether they will also be cured with such inflammation. According to the findings of this systematic review, it is especially important to start observing the phenomena of inflamed AK in patients treated with taxanes, pemetrexed, and doxorubicin.

The main limitation of our systematic review is that it combines data across case reports and case series, leading to very low quality of evidence, for example, well-known publication bias inherent in case reports. Next, the reporting of the outcome of inflamed AK differed between the included articles, so it cannot be ruled out that some authors, when describing the outcome, actually reported the resolution of inflammation and not regression of AK. An additional limitation of this manuscript is that certain chemotherapeutic agents or combinations of them are associated with isolated cases of AK inflammation, which could also be a consequence of other as yet unidentified factors.

In conclusion, evidence suggests the potential for repositioning other chemotherapeutics for the management of AK, highlighting the need for further studies, especially focused on the potential development of topical products from taxanes, pemetrexed, and doxorubicin.

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Additional material (Excel Sheet) is available upon request.

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