Acneiform eruptions with combination targeted cancer therapy in colorectal cancer patients

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Research Article

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Abstract

Purpose:

Epidermal growth factor receptor inhibitors (EGFRI) can be used with pathway inhibitors, including mitogen-activated protein kinase kinase inhibitors (MEKIs), BRAF inhibitors (BRAFIs), and checkpoint inhibitors such as programmed death-ligand 1 (PD-L1) and programmed cell death protein 1 (PD-1) to treat colorectal cancer. These can precipitate treatment-resistant acneiform eruptions, prompting dose modification or discontinuation. Predicting the likelihood of severe rash development and crafting effective treatments may promote adherence to life-saving chemotherapy.

Methods:

An Institutional Review Board approved retrospective chart review of patients with colorectal cancer treated with EGFRI or MEKI in combination with HER2, BRAF, PI3K, or checkpoint inhibitors between January 1, 2016 and January 1, 2020 was performed. Surrogates for rash severity were investigated, including lower extremity involvement, utilization of oral steroids or retinoids, dose modification, and incidence of superinfection.

Results:

Of 122 patients treated with combination therapy, 105 developed a rash, and 87 developed an acneiform eruption. Common combinations included MEKI/PD-LI, EGFRI/MEKI, and MEKI/PD-1I. Patients treated with EGFRI/MEKI developed the most severe rashes (p=0.02). Lower extremity involvement was more frequent with EGFRI/MEKI compared to alternative combinations (p=0.05). Drug holiday correlated with all rash severity surrogates, including rash grade, lower extremity involvement, oral steroid or retinoid use, and incidence of superinfection. Use of oral steroids or retinoids was associated with development of superinfection (p=0.002). Prophylactic tetracycline use did not impact rash severity or rash incidence.

Conclusion:

This is the first descriptive analysis to characterize acneiform eruptions for patients with colorectal cancer on combination cancer therapy. Approximately 85% of patients developed a cutaneous toxicity with, what appears, to be synergistic effects of EGFRI and MEKI combination therapy causing the most severe eruptions. Superinfection rate correlated to systemic therapy use beyond oral tetracyclines. Further investigation into the utility of prophylactic oral tetracyclines in this population is needed.

Introduction

Epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein that is a member of the ErbB receptor tyrosine kinase family. Activation of this receptor regulates tumor cell differentiation and survival and can lead to enhanced uncontrolled cellular proliferation.[1,2] In recent years, pharmacologists have developed therapies targeting this cascade known as EGFR inhibitors (EGFRIs). EGFRIs were initially

approved by the U.S. Food and Drug Administration (FDA) for treatment of non-small-cell lung cancer.[3] Today, the agents are routinely used for head and neck, pancreatic, colorectal, and breast cancers with appropriate markers.[4,5]

Although EGFRI therapy has been effective in managing various malignancies, monotherapy may not be enough for a subset of therapy-resistant cancers.[6] For these cases, combination therapy of EGFRIs with other pathway inhibitors including mitogen-activated protein kinase kinase inhibitors (MEKIs), BRAF inhibitors (BRAFIs), and checkpoint inhibitors such as programmed death-ligand 1 (PD-L1) and programmed cell death protein 1 (PD-1) inhibitors have demonstrated high tumor response rates.[7,8] These combinations are being further tested in over twenty cancer clinical trials. While EGFRI therapies in combination with these pathway inhibitors have shown promise in achieving tumor remission, they also precipitate a number of adverse events (AEs), with a vast majority of patients (90–100%) experiencing at least one AE.[9–11]

The most common AE associated with these therapies is cutaneous acneiform eruption. These lesions manifest as follicular papules, nodules, and pustules. They typically form within the first two weeks of EGFRI treatment and commonly affect the scalp, face, upper chest, and back.[12] With EGFRI monotherapy, acneiform eruptions develop in 65 to 90% of all treated patients.[2] MEKIs, BRAFIs, and checkpoint inhibitors are also associated with similar skin eruptions, reported in 67.5 to 71% of patients.[9–11] In addition to acneiform eruptions, these same drug classes are known to cause paronychia, inflammation of the nailfold. The incidence in association with EGFRI therapy ranges from 3–57%, and paronychia has a later onset and more prolonged course compared to acneiform eruptions.[13] The degree of toxicity of these cutaneous AEs (CAEs) has been reported to correlate with increasing inhibitor doses and treatment duration in patients with solid tumor malignancies such as colorectal and non-small cell lung cancers.[12,14]

The growing use of combination therapy of EGFRIs with MEKIs, BRAFIs, and checkpoint inhibitors have made CAEs more difficult to manage, as patients are presenting with severe, treatment-resistant eruptions. These lesions can deleteriously impact patients' quality of life.[15] Furthermore, in severe cases, life-prolonging combination therapy may be dose reduced or discontinued in order to avoid this side effect. Given the impact of these CAEs, predictive markers for severe CAEs and effective management strategies have become increasingly important for drug tolerability and compliance. Therefore, although a majority of patients on EGFRI therapy develop acneiform eruptions, it is vital to identify patients at risk of developing severe eruptions, to develop effective management strategies, and to determine how the severity of acneiform eruption correlates with EGFRI combination treatment efficacy.

To this end, we sought to identify predictive factors to help anticipate the severity of acneiform eruptions, guide management of CAEs, and explore their correlation with tumor responsiveness. Such models have been validated for a number of diseases, and can assist with guiding clinical decision-making and patient counseling.[16]

Materials And Methods

Identification of Patients

Upon receiving approval from the Institutional Review Board of MD Anderson, we identified patients between January 1, 2016 and January 1, 2020 who had been treated with a combination acneiform eruption- inducing therapy by utilizing our institutional pharmacy database. This included EGFRI or MEKI in combination with HER2, BRAF, PI3K, or checkpoint inhibitors. This cohort was further filtered for a visit diagnosis code of colon cancer (ICD-10 C18.*). We focused on this population as, anecdotally, they use combination therapy most frequently, have the most severe CAEs, and are the most difficult to manage.

All patient charts were manually reviewed to confirm the above diagnosis and treatment in the desired timeframe. Data collected included patient characteristics such as age, sex, primary cancer type, prior cancer therapy exposures, prior AEs, co-morbidities, and medications. Information regarding the tumor staging and response, treatment timing and dosing, and CAE timing and management were gathered. Diagnostic criteria for acneiform eruptions as described by Welborn et al was utilized and included: Documentation by a board-certified dermatologist or meeting two of the four following clinical criteria from chart documentation: (I) description of follicular papules/pustules, (II) description of acneiform or acne-like, (III) pictures of rash consistent with acneiform eruption, and (IV) distribution that involves the face and arms.[10] The severity of acneiform eruptions was graded on a scale of 1 to 5, as delineated by the Common Terminology Criteria for Adverse Events (CTCAE).[17]

Statistical Analysis

Quantitative data were analyzed with descriptive and inferential statistics, including Fisher exact tests for categorical variables and ANOVA or two-tailed unpaired student's t-tests for continuous variables. Analyses were performed using GraphPad PRISM 9 (La Jolla, CA). Statistical significance was set at $p < 0.05$.

Results

We identified 122 patients who were treated with EGFRI or MEKI in combination with other chemotherapeutic agents. Patient demographics data are summarized in Table 1. Sixty-eight males and fifty-eight females with a mean age of 57 (range 31–76) received combination therapy for a duration of 12weeks on average (range 1-107); the majority (101 patients, 83%) received treatment for stage IV colon cancer. Median prior lines of treatment were 3 (range 1–10).

Table 1
Patient Demographics

Age (yrs at time of treatment initiation)	**Years, median (range)**	**57 (31–76)**
Sex	Male, n	68
	Female, n	54
Ethnicity	White/Caucasian	98
	Hispanic/Latino	12
	Black/African American	4
	Asian	7
	Other	1
Primary cancer type/location	Left	59
	Right	56
	Transverse	7
Cancer stage at time of diagnosis	Stage II	3
	Stage III	12
	Stage IV	101
	unknown	6
WNT mutations	*KRAS*, n	61
	NRAS, n	8
	BRAF, n	27
	APC, n	58
	PIK3CA, n	34

Legend:

Yrs = years, WNT = wingless/integrated, *KRAS* = Kirsten rat sarcoma virus oncogene, *NRAS* = neuroblastoma RAS viral oncogene, *BRAF* = v-raf murine sarcoma viral oncogene homolog B1, *APC* = adenomatous polyposis coli gene, *PIK3CA* = Phosphatidylinositol-4,5-bisphosphate 3-kinase gene, EGFRI = Epidermal growth factor receptor inhibitor, MEKI = mitogen-activated protein kinase kinase inhibitor, BRAFI = BRAF inhibitor, PD-L1 = programmed death-ligand 1 (PD-L1), PD-1 = programmed cell death protein 1

Age (yrs at time of treatment initiation)	**Years, median (range)**	**57 (31–76)**
Prior lines of treatment	Median (range)	3 (0–10)
Prior acne-inducing drug exposure	EGFRI, n	8
	MEKI, n	1
	PD1I, n	2
	CTLA4I, n	1
	PD-L1I, n	0
Weeks on combination therapy	Median (range)	12 (0-107)
Legend:		
Yrs = years, WNT = wingless/integrated, *KRAS* = Kirsten rat sarcoma virus oncogene, *NRAS* = neuroblastoma RAS viral oncogene, *BRAF* = v-raf murine sarcoma viral oncogene homolog B1, *APC* = adenomatous polyposis coli gene, *PIK3CA* = Phosphatidylinositol-4,5-bisphosphate 3-kinase gene, EGFRI = Epidermal growth factor receptor inhibitor, MEKI = mitogen-activated protein kinase kinase inhibitor, BRAFI = BRAF inhibitor, PD-L1 = programmed death-ligand 1 (PD-L1), PD-1 = programmed cell death protein 1		

Of 122 patients treated with combination therapy, 105 patients (86%) developed a rash, and 87 patients (71%) developed an acneiform eruption specifically (Table 2). Eleven patients (9%) developed paronychia; of these, 8 (73%) also developed acneiform eruptions. Ten patients (8%) developed eczema, and 5 (50%) of those patients developed acneiform eruptions. Median days to rash onset from combination therapy initiation was 14 (range 0 -851). Seventy-five patients (62%) received dose modification due to their rashes, and of those, twenty-eight (37%) patients had drug holidays with a mean of 24 days (range 1–88). Twenty-seven patients (36%) had dose reductions alone, ten (13%) patients had dose reductions followed by discontinuation, and ten (13%) patients had discontinuation alone. Of 87 patients with acneiform eruptions, 82 patients (94%) had head and neck involvement, 64 (74%) had trunk involvement, 30 (35%) had bilateral upper extremity involvement, and 14 (16%) had bilateral lower extremity involvement. Of 11 patients with superinfections, 7 (64%) had acneiform eruption, while 4 (36%) had paronychia. For cancer outcome, 117 (96%) experienced tumor progression, 2 (0.02%) had stable disease, 2 (0.02%) had improvement, and 1 (0.01%) was lost to follow-up.

Table 2
Rash characteristics

Acneiform	**pts with rash, n**	**87**
Paronychia	pts with acneiform, n	8
n = 11	pts without acneiform, n	3
Eczema	pts with acneiform, n	5
n = 10	pts without acneiform, n	5
Days to rash onset (acneiform)	median, mean (range)	14, 34 (0–851)
Dose impact secondary to rash, n = 53	total # pts with holiday n, mean (range) d.*	28, 24 (1–88)
	pts with holiday alone, n	7
	pts with reduction alone, n	29
	pts w/ discontinuation alone, n.	9
	pts with reduction then discontinuation	8
Acneiform rash distribution (non-mutually exclusive)	Head/Neck, n	82
	Trunk, n	64
	Bilateral upper extremities, n	30
	Bilateral lower extremities, n	14
Superinfection	Acneiform, n	7
	Paronychia, n	4
Symptoms	Pruritus, n	38
	Pain, n	14
	Bleeding, n	6
Treatment	PO tetracyclines, n	93
	PO steroid, n	13
	PO retinoid, n	6

Legend:

pt = patient, pts = patients, d = days, mos = months, PO = per oral

* indicates overlap with reduction or discontinuation criteria

Acneiform	pts with rash, n	87
Doxycycline treatment n = 93	Prophylactic use, n = 32 no rash, n; rash persist > 5 mos, n; resolved by 5 mos, n	6, 8, 18
	Therapeutic use, n = 61 rash persist > 5 mos, n; resolved by 5 mos, n	18, 43
Rash outcome	1 month improved, n; total patients = 105	47 (44.8%)
	3 month improved, n; total rash patients = 73	38 (52.1%)
	5 month improved, n, total rash patients = 47	17 (36.2%)
Reason stopped	progression, n	90
	toxicity skin, n	17
	competed treatment, n	10
	toxicity non-skin, n	3
Tumor outcome	progression, n	117
	stable, n	2
	improved, n	2
Legend:		
pt = patient, pts = patients, d = days, mos = months, PO = per oral		
* indicates overlap with reduction or discontinuation criteria		

Neither age, sex, tumor location, tumor mutation, nor prior exposure to EGFRI or other prior acne-inducing therapy significantly correlated with incidence of rash. In contrast, two-way ANOVA comparing incidence of rash across various types of combination therapies revealed that treatment type was associated with rash development ($p = 0.04$). The most commonly utilized combination therapies included MEKI/PD-L1I, EGFRI/MEKI, MEKI/PD-1I (Table 3).

Table 3
Most frequently used combination therapies and rash incidence

Combination Therapy	pts on therapy, n	pts w/ rash, n (%)
MEKI/PD-L1I	37	27 (73%)
EGFRI/MEKI	22	19 (86%)
MEKI/PD-1I	12	8 (67%)
MEKI/HER2I	5	3 (60%)
MEKI/pan-ErbBI	3	3 (100%)
EGFRI/CD47I	2	2 (100%)
EGFRI/BRAFI	1	1 (100%)
EGFRI/PDLI	1	1 (100%)

EGFRI = Epidermal growth factor receptor inhibitor, MEKI = mitogen-activated protein kinase kinase inhibitor, BRAFI = BRAF inhibitor, PD-L1I = programmed death-ligand 1 inhibitor, PD-1I = programmed cell death protein 1 inhibitor, HER2I = human epidermal growth factor receptor 2 inhibitor, pan-ErbBI = pan ERbB inhibitor, CD47I = cluster of differentiation 47 inhibitor

Severe rash, which is defined as CTCAE grade 3 or 4 rash, can also have clinically-relevant surrogates such as lower extremity involvement, utilization of oral steroids or retinoids, need for dose modification (i.e. drug holiday, dose reduction, or drug discontinuation), and incidence of superinfections (Table 4). When comparing the relationship amongst these surrogate markers, patients who experienced any form of dose modification (e.g., drug holiday, dose reduction, or drug discontinuation) were significantly more likely to have a higher grade rash and lower extremity involvement ($p < 0.001$ and $p = 0.002$, respectively). In particular, drug holiday strongly correlated with all markers of rash severity including rash grade, lower extremity involvement, oral steroid or retinoid use, and incidence of superinfection ($p < 0.001$, $p = 0.009$, $p = 0.029$, $p = 0.001$). Drug dose reduction correlated with rash grade, lower extremity involvement, and incidence of superinfection ($p < 0.001$, $p = 0.013$, $p = 0.041$); it did not correlate with utilization of oral steroids or retinoids.

Table 4
Predictive Factors and Severity Markers of Acneiform Eruptions

	Markers of Severity					
possible predictive factors	**incidence of rash**	**rash grade (III or IV)**	**dose modification**	**use of oral steroids or retinoids**	**Lower extremity involvement**	**Superinfection incidence**
age	p = 0.5	p = 0.2	p = 0.67	p = 1	p = 0.4	p = 1
sex	p = 0.2	p = 0.9	p = 0.1	p = 0.2	p = 0.2	p = 0.3
ethnicity (white vs non-white)	p = 0.3	N/A	N/A	N/A	N/A	N/A
PMHx of skin disease	p = 0.4	N/A	N/A	N/A	N/A	N/A
prior EGFRi exposure	p = 0.6	p = 0.3	p = 0.8	p = 0.6	p = 0.01	p = 0.4
prior acne-inducing drug	p = 0.7	p = 0.3	p = 0.7	p = 0.4	p = 0.3	p = 0.6
prior cutaneous toxicity to chemotherapy	p = 0.417	N/A	N/A	N/A	N/A	N/A
number of previous lines of therapy	p = 0.591	N/A	N/A	N/A	N/A	N/A
cancer location	p = 0.8	p = 0.8	p = 0.8	p = 0.6	p = 1	p = 1
cancer mutation type(s)	p = 0.4	p = 0.3	p = 0.4	p = 0.3	p = 0.6	p = 1
any type of combination therapy	p = 0.04	N/A	N/A	N/A	N/A	N/A
MEKI/EGFRI treatment	N/A	p = 0.02	p = 0.8	p = 0.7	p = 0.05	p = 0.2
rash onset (< 2 weeks vs > 2 weeks)	N/A	p = 0.03	p = 0.3	p = 0.01	p = 0.4	p = 0.01
paronychia	p = 0.2	N/A	N/A	N/A	N/A	N/A
eczematous dermatitis	p = 0.4	N/A	N/A	N/A	N/A	N/A

Markers of Severity						
pain	N/A	p < 0.001	p = 0.002	p = 0.08	p < 0.001	p < 0.001
pruritus	N/A	p = 0.2	p = 0.5	p = 0.8	p = 0.5	p = 0.7
bleeding	N/A	p < 0.001	p = 0.004	p = 0.3	p = 0.3	p = 0.1
drug holiday of any duration	N/A	p < 0.001	N/A	p = 0.03	p = 0.009	p = 0.001
drug holiday < 30 days vs > 30 days	N/A	p = 0.1	N/A	p = 1	p = 0.6	p = 0.6
1 or > 1 drug holiday	N/A	p = 0.8	N/A	p = 1	p = 1	p = 0.2
drug dose reduction	N/A	p < 0.001	N/A	p = 0.2	p = 0.01	p = 0.04
dose modification of any kind	N/A	p < 0.001	N/A	p = 0.1	p = 0.002	p = 0.09
days on tetracycline (< 200 or > 200)	N/A	N/A	p = 0.02	p = 0.7	p = 0.3	p = 1
prophylactic tetracycline	p = 0.6	p = 0.5	p = 0.8	p = 1	p = 0.5	p = 0.6
tetracycline alongside rash onset vs after rash development	N/A	p = 0.7	p = 0.3	p = 1	p = 0.4	p = 0.7

Age, sex, tumor location, and presence of pruritus did not correlate with rash severity. No correlation was found between combination therapy and rash severity as measured by oral steroid or retinoid use, dose modification, or incidence of superinfection. Among those who did develop a rash while on combination therapies, those treated with EGFRI/MEKI developed the most severe rashes ($p = 0.02$). Additionally, instances of lower extremity involvement were significantly more frequent in those treated with EGFRI/MEKI compared to those patients receiving alternative combination regimens ($p = 0.05$).

For patients with rash, time to rash onset of less than two weeks after initiating combination therapy was associated with more severe rash ($p = 0.03$). Earlier rash onset was also associated with the need for oral steroid or retinoid use, as well as increased incidence of superinfection ($p = 0.01$ for each). No associations were found among time to rash onset, lower extremity involvement, and dose modification.

Both pain and bleeding were found to correlate with rash grade and dose modification, though only pain was associated with an incidence of superinfection (all $p < 0.004$).

Other associations were observed when examining treatment options utilized for acneiform eruptions. Though only 16 patients with acneiform eruptions were placed on oral steroids or retinoids, a strong association was observed between these medications and subsequent development of superinfection ($p = 0.002$). Additionally, utilization of tetracyclines beyond 200 days was associated with decreased instances of dose reduction ($p = 0.024$). Despite this, prophylactic utilization of tetracycline did not significantly impact any marker of rash severity nor incidence of rash.

No correlation was found between treatment regimen and development of eczematous dermatitis or paronychia.

Discussion

While previous studies have highlighted the association between MEKI or EGFRI on the development of acneiform eruptions, this study is the first descriptive analysis examining the relationship between combination therapy, potential predictive factors, the development of acneiform eruptions and other less common cutaneous AEs, and management strategies in patients with colon cancer.

In our cohort, 71% of patients on combination therapy developed acneiform eruptions. This finding is comparable to findings of EGFRI or MEKI monotherapy precipitating acneiform eruptions in 60–90% or 63%-77% of patients, respectively.[2,18,19] Most commonly utilized two-drug combinations in our cohort included MEKI/PD-LI, EGFRI/MEKI, and MEKI/PD-1I; 73.0%, 86%, and 67% of patients on these regimens, respectively, developed acneiform eruptions. Notably, those placed on MEK/EGFRI developed the most severe rashes, and prior exposure to EGFRI monotherapy or other acne-inducing chemotherapies were not associated with either rash development nor severity. These points underscore the importance and difficulty inherent in prudent combination therapy selection, as medications that patients may have previously tolerated well as separate lines of therapy may precipitate adverse cutaneous reactions when paired together.

Based on previous findings, acneiform eruption typically occur within one to two weeks of treatment for either EGFRI or MEKI monotherapy.[12,19–23] This is comparable to what was observed in our cohort; the median time from combination therapy initiation to acneiform eruption onset was 14 days. The distribution of acneiform eruptions in EGFRI or MEKI monotherapy compared to combination therapy is another area of note. In EGFRI or MEKI monotherapy, acneiform eruptions are typically restricted to the face, scalp, chest, and upper trunk.[20,24] While in our cohort, the face and upper trunk remain predominantly affected, 35% of patients with acneiform eruption experienced bilateral upper extremity involvement, while 16% of acneiform eruption patients developed bilateral lower extremity involvement. This atypical distribution is seldomly reported with monotherapy and can greatly affect patients' pain level and cancer therapy compliance. The rapidity of rash development, the extensive rash distribution

seen with combination therapy, and increased severity all emphasize the need for physician vigilance and preventative therapy.

Once the acneiform eruption has been observed, oncologists may opt for dose modification, including dose reduction with or without a drug holiday or discontinuation. In our cohort, 75 (61%) patients underwent dose modification. The most common modifications included drug holidays and dose reduction without discontinuation for 28 (23%) and 27 (22%) patients, respectively, though treatment was ultimately discontinued for 20 (16%) patients; 17 of these patients discontinued medication due to cutaneous toxicity, second only to discontinuation due to disease progression. In contrast, a study of EGFRI monotherapy revealed far less instances of dose modification; 14% of patients required treatment interruption, 12% required dose reduction due to rash, and 5% discontinued the medication.[25] Rash severity, distribution, or patient intolerance of the rash's associated symptoms may have triggered discontinuation.[26] This, too, is echoed in our findings, as forms of dose modification (e.g., drug holiday, dose reduction, or drug discontinuation) correlated with rash severity and other surrogate markers such as lower extremity involvement and accompanying symptoms.

Symptoms such as pruritus, pain, or spontaneous bleeding accompanied acneiform eruptions in 58 (67%) patients; pruritus was the most common symptom. Unlike pruritus, both pain and spontaneous bleeding correlated with rash severity, as did the development of superinfections. In our cohort, though 11 patients developed superinfection and 64% of them had an acneiform eruption, none required combination therapy discontinuation secondary to superinfection. These findings emphasize several key points. Firstly, decoupling pruritus from the acneiform eruption may be beneficial for patients when assessing and treating the cutaneous toxicities precipitated by combination therapy. Secondly, early recognition and management of both severe acneiform eruptions and their associated symptoms such as pain and bleeding are imperative for maximizing utilization and preventing premature discontinuation of potentially life-saving chemotherapy.

Treatment for combination therapy-associated acneiform eruption has not yet been established. In our cohort, treatment regimens mimicked treatments utilized for patients with EGFRI-associated acneiform eruption, including topical steroids, oral antibiotics, or oral retinoids. Depending on the severity of the rash, topical therapies may sufficiently address the rash; however, oral tetracyclines such as minocycline and doxycycline can be added for rash grade 2 or above. Indeed, tetracyclines have even been examined for prophylactic use in several randomized control trials. While two studies did not reveal a significant benefit, multiple studies have shown a decrease in eruption severity and improvement in patients' quality of life.[27] In our study, prophylactic tetracycline use did not appear to impact rash severity or rash incidence. Regardless, tetracyclines have become a fixture of management in the setting of EGFRI-associated acneiform eruption.

In contrast to the literature on tetracycline use, data regarding the utility of oral retinoids is limited; however, small studies investigating oral isotretinoin and oral acitretin use in EGFRI-associated acneiform eruptions have shown improvements among limited cohorts of patients.[27–31] In our study, of 105

patients who developed a rash, the vast majority (93, 89%) were treated with tetracyclines. Only 6 patients received an oral retinoid. Of these, 5 initiated acitretin, and 1 received isotretinoin. Four patients had rash resolution by 5 months post rash appearance, 1 patient experienced continuous improvement without full resolution, and 1 patient improved for 8 months before again worsening. No patients reported significant adverse events stemming from oral retinoid use, even in the setting of liver metastases. Only 1 patient did not experience improvement, and chart review noted that rash worsening also coincided with the initiation of trimethoprim/sulfamethoxazole for another condition. Based on these observations in this small subset of our cohort, oral retinoids may be beneficial for treatment of combination therapy-associated acneiform eruptions, although patients should be monitored closely for potential superinfections.

Symptoms associated with rash severity in this cohort include utilization of MEKI/EGFRI combination therapy, development of lesions on the bilateral lower extremities, and development of bleeding, pain, and superinfections. These factors are associated with dose modifications of cancer therapy (dose reduction with or without a drug holiday or discontinuation) and rash requiring treatment with oral retinoids or steroids. The early recognition of these factors and the aggressive treatment of the rashes could possibly decrease the need for cancer therapy dose modifications. Prospective studies for rash prophylaxis in this population of MEKI/EGFRI treated colorectal cancer patients would be valuable.

Limitations

This study has several limitations. The patient data was collected from a comprehensive cancer center whose patient population is not reflective of the general population. Indeed, the majority of patients in this cohort had stage IV colon cancer who had failed multiple lines of therapy prior to initiating combination therapy; 105 of the 122 patients attempted an experimental clinical trial as one of their final lines of treatment. Similarly, in our cohort, the majority (90/122) of patients discontinued combination therapy due to cancer progression, further emphasizing the aggressive and nonresponsive nature of their disease. Based on these points, it is difficult to conduct meaningful statistical analysis that elucidates the relationship between acneiform eruptions and tumor response. Other areas for exploration, such as the relationship among paronychia, eczema, and combination therapy could not be elucidated due to their infrequent manifestation in this patient population. Additionally, because of the nature of the retrospective analysis and chart review, we were limited to data documented in the electronic medical record.

Conclusion

Our study is the first, to our knowledge, to have conducted a descriptive analysis of acneiform eruptions triggered by EGFRI or MEKI utilized in combination for treatment of colon cancer. When compared to EGFRI or MEKI monotherapy, combination therapy demonstrates comparable incidence and timing of acneiform eruption development, though these eruptions manifest more extensively and symptomatically, resulting in greater instances of dose reduction, drug holiday, or dose discontinuation. This study also offers potential treatment strategies that can be pursued, such as tetracyclines and oral retinoids,

highlighting the importance of a multidisciplinary approach to oncologic care that includes dermatology and the need for better therapeutic options for acneiform eruptions. A study utilizing prophylactic oral retinoids may be fruitful potentially. Further research exploring combination therapy may uncover optimal treatment strategies that will allow patients to continue potentially life-saving chemotherapy while minimizing the common and debilitating cutaneous adverse events observed.

Declarations

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Authors' contributions:

Marina K Ibraheim: Investigation (equal); Data curation (equal); Writing original draft (equal); Writing-review and editing (lead); Project administration (lead)

Jonathan Lo: Investigation (equal); Data curation (equal); Writing original draft (equal)

Rohit Gupta: Investigation (equal); Data curation (equal); Formal analysis (lead)

Christine Parseghian: Conceptualization (equal); Writing-review and editing (equal)

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