The effect of cytotoxic chemotherapy on the risk of high-grade acneiform rash to cetuximab in cancer patients: a meta-analysis

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Received 13 October 2010; revised 4 January 2011; accepted 10 January 2011

Background: The effect of chemotherapy on the risk of cetuximab-induced acneiform rash is unknown. We carried out a systematic review and meta-analysis of published studies to quantify the incidence and risk of high-grade acneiform rash with combination therapy.

Methods: Relevant studies were identified from PubMed database, abstracts presented at the American Society of Clinical Oncology conferences, and Web of Science. Incidence of acneiform rash to cetuximab monotherapy was estimated based on updated data from our previously published meta-analysis. Incidence, relative risk (RR), and 95% confidence intervals (CIs) were calculated based on the heterogeneity of included studies.

Results: A total of 5333 patients from nine trials were included in the analysis. The incidence of high-grade acneiform rash was significantly increased in patients receiving combination treatment (12.8%, 95% CI 9.1% to 17.7%) as compared with cetuximab monotherapy (6.3%, 95% CI 3.7% to 10.5%), with a risk ratio of 2.03 (95% CI 1.52–2.71, \( P < 0.01 \)). Cetuximab significantly increased the risk of high-grade rash in patients receiving combination therapy (RR = 37.7, 95% CI 17.8–80.0, \( P < 0.001 \)).

Conclusions: Addition of cytotoxic chemotherapy to cetuximab significantly increases the risk of high-grade acneiform rash compared with cetuximab monotherapy. This emphasizes the need for effective management strategies.

Key words: acneiform rash, cetuximab, cytotoxic chemotherapy, papulopustular rash
[24]. Despite the increased use of combination therapy, the effect of cetuximab-induced papulopustular rash is currently unknown. We conducted a systematic review of the literature to identify published clinical trials of cetuximab in combination with chemotherapy and carried out a meta-analysis to determine the overall incidence and risk of developing a rash, with a focus on high-grade acneiform rash to combination therapy. In our secondary analysis, we also explored the difference between the overall incidence of high-grade acneiform rash in patients receiving combination therapy and in those treated with cetuximab monotherapy.

methods

data source
An independent search of citations was conducted using the PubMed database (1998 to January 2010). The keywords ‘cetuximab’, ‘chemotherapy’, and ‘combination’ were used in the search, which was limited to human, randomized, controlled phase II and III clinical trials (RCTs). We also searched abstracts containing the terms ‘cetuximab’ and ‘randomized’ presented at the American Society of Clinical Oncology (ASCO) conferences (2004 and January 2010) to identify relevant clinical trials. An independent search using the Web of Science database (a product developed by the Institute for Scientific Information, a citation database) was conducted to ensure that no additional relevant studies have been missed. We reviewed each publication, and only the complete or the most recent report of a clinical trial was included when duplicate publications of the trial were identified. For the secondary analysis, in which the incidence of high-grade acneiform rash to cetuximab monotherapy was estimated, we used the published articles of clinical trials included in our previous meta-analysis [24], which met our current inclusion criteria. However, to ensure data accuracy and include the most updated results, we searched PubMed database to identify if any of the ASCO abstracts included in our previous meta-analysis were published. Updated manufacturer package insert of cetuximab was also reviewed for related information. Details on study characteristics, treatment information, results and safety profiles from selected studies were extracted.

study selection
Only RCTs with a comparison between cetuximab combined with cytotoxic chemotherapy and a control without cetuximab were included for analysis. Cetuximab has been approved for mCRC in combination with irinotecan at a starting dose of 400 mg/m² followed by 250 mg/m² weekly. To ensure practical significance, we determined the risk of an acneiform rash in cancer patients receiving combination therapy with cetuximab at this dose level. Phase I trials and single-arm phase II trials were excluded from the analysis due to multiple dose levels and lack of controls, respectively. The trials that met the following criteria were selected for the final analysis: (i) prospective phase II and III RCTs in cancer patients; (ii) patients randomly assigned to be treated with cetuximab at the starting dose of 400 mg/m² followed by 250 mg/m² weekly in combination with cytotoxic chemotherapy agents or control arm without cetuximab; and (iii) data available for the incidence of an acneiform, acne or acne-like skin rash and sample sizes.

clinical end points
Clinical end points including acneiform, acne-like, and acne rash were selected from the safety profiles of each clinical trial. The included studies reported the incidence of acneiform rash of grade 1–5 (all grade) or grade ≥3 (high grade). These toxic effects were documented according to versions 2 or 3 of the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI). The grading of a skin rash in version 2.0 is described as the following: grade 1, macular or papular eruption or erythema without associated symptoms; grade 2, macular or papular eruption or erythema with pruritus or other associated symptoms, localized desquamation or other lesions covering <30% of the body surface area (BSA); grade 3, severe generalized erythromeda or macular, papular or vesicular eruption, desquamation covering ≥50% BSA; grade 4, generalized exfoliative, ulcerative, or bullous dermatitic; and grade 5, death. An additional category of acne/acneiform rash is only described in version 3.0 as the following: grade 1, intervention not indicated; grade 2, intervention indicated; grade 3, associated with pain, disfigurement, ulceration, or desquamation; no grade 4; and grade 5, death.

statistical analysis
All statistical analyses were done using version 2.0 of the Comprehensive Meta-Analysis program (Biostat, Englewood, NJ). The numbers of patients with all-grade and high-grade (≥3) acneiform, acne-like, and acne rash were extracted from selected trials as described above. For each trial, the incidence of acneiform rash was calculated, and the 95% confidence interval (CI) was derived. The relative risk (RR) of acneiform rash among patients assigned to cetuximab in combination with chemotherapy was calculated and compared only with that of patients assigned to a control treatment in the same trial.

For meta-analysis, both the fixed-effects model (weighted with inverse variance) and the random-effects model were considered. For each meta-analysis, Cochran’s Q statistic was first calculated to assess the heterogeneity of the included trials. For P values <0.1, the assumption of homogeneity was deemed invalid, and the random-effects model was used. Otherwise, results from both the fixed-effects model and the random-effects model were evaluated. If the results of the fixed-effects and the random-effects model were similar, only fixed-effects model results were reported. A two-tailed P value of <0.05 was considered as statistically significant.

results

search results
Our search yielded a total of 219 potentially relevant clinical studies on cetuximab combined with chemotherapy (Figure 1). PubMed search identified 130 articles and we excluded 115, leaving 15 trials for a full review. Subsequently, seven studies were excluded, in which skin toxicity was categorized as ‘rash’, ‘rash/desquamation’, ‘skin reactions’, or ‘skin toxicity’. After final screening, eight original trials met our inclusion criteria [13, 17, 19, 20, 25–28]. These studies included phase II and III RCTs. Our search of ASCO abstracts yielded 89 potentially relevant studies, of which 1 study met our inclusion criteria [29]. We have included nine RCTs in our final analysis (Table 1). The PubMed search for any published ASCO abstracts included in our previous meta-analysis of cetuximab monotherapy yielded four articles that have since been published [30–33]. However, one was excluded since skin toxicity was categorized as ‘rash/desquamation’ [31]. Therefore, for our secondary analysis of the incidence of high-grade acneiform rash associated with cetuximab monotherapy, six studies have been included (Table 2) [10, 12, 30, 32, 34, 35].

patients
A total of 5333 patients from nine clinical trials were analyzed, of which 2664 received treatment with cetuximab in
combination with chemotherapy agents (Table 1). The chemotherapeutic agents used in these trials included gemcitabine in combination with cisplatin or carboplatin [25], cisplatin in combination with 5-fluorouracil (5-FU) [20], paclitaxel or docetaxel in combination with carboplatin [26], 5-FU combined with leucovorin and oxaliplatin (FOLFOX-4) [29], cisplatin with vinorelbine [19, 27], single-agent irinotecan [28], capcitabine combined with oxaliplatin and bevacizumab [17], and irinotecan combined with 5-FU and leucovorin (FOLFIRI) [13]. Underlying malignancies included non-small-cell lung cancer (NSCLC) (four trials), mCRC (four trials), and esophageal squamous-cell carcinoma (one trial). An acneiform rash was not mentioned as a preexisting condition in selected trials. The follow-up time was specified only in four trials [13, 17, 20, 27]. In all selected RCTs, patients were assigned to receive cetuximab in combination with chemotherapy or a control arm with chemotherapy only.

incidence of all-grade acneiform rash

Data for all-grade acneiform rash were available from a total of 1324 patients receiving cetuximab in combination with chemotherapy agents [19, 20, 25, 27, 28]. The incidences of all-grade acneiform rash ranged between 68.8% and 76.3%, with the highest incidence observed in a phase III RCT in patients with mCRC [28]. According to the fixed-effects model, the overall incidence of all-grade acneiform rash was 73.1% (95% CI 70.7% to 75.5%).

incidence of high-grade acneiform rash

High-grade (grade ≥3) skin reactions result in patient morbidity, treatment cessation, or dose modifications. The incidence of high-grade acneiform rash ranged from 6.3% to 25.4%, with the highest incidence observed in patients with mCRC [17]. According to the random-effects model, the overall incidence of high-grade acneiform rash was 12.8% (95% CI 9.1% to 17.7%), based on nine RCTs with a total of 2664 patients (Figure 2).

incidence of high-grade acneiform rash with combination treatment in patients with mCRC, non-CRC, and other tumor types

Because the highest incidence of acneiform rash was observed in mCRC patients, we further determined the incidence of high-grade acneiform rash in mCRC patients and non-colorectal cancer (CRC) separately. The incidences of high-grade acneiform rash in mCRC and non-CRC patients were 15.9% (95% CI 9.3% to 25.8%) and 10.5% (95% CI 8.7% to 12.5%), respectively, but this difference did not reach statistical significance ($P = 0.254$). Meta-analysis showed that RR in mCRC and non-CRC patients was 51.4 (95% CI 19.2–138.0) and 24.2 (95% CI 7.6–77.5) according to the fixed-effects model, respectively, without reaching statistical significance ($P = 0.33$) (Table 3). Interestingly, there was significant variation for the incidence of high-grade acneiform rash among different tumor types ($P < 0.01$). However, no
significant variation of RRs with combination treatment was observed among different primary tumors \( (P = 0.32) \).

**RR of acneiform rash**

To investigate the specific contribution of cetuximab to the development of acneiform rash and exclude the influence of confounding factors, we have determined the RR from combination therapy. A pooled analysis of the RR of all-grade acneiform rash associated with combination treatment was carried out from five RCTs, in which its incidence was reported in 2654 patients, among which 1324 received combination therapy and 1330 received only chemotherapy. Similarly, a pooled analysis of the RR of high-grade acneiform rash with combination treatment was carried out from nine RCTs, in which the incidence was reported in 5333 patients, among which 2664 received combination therapy and 2669 received control treatment only. A meta-analysis showed that RR was 11.4 with combination treatment versus control for all-grade acneiform rash \( (95\% \text{ CI 7.4–17.6}, P < 0.001) \), according to the random-effects model, and 37.7 for high-grade acneiform rash.

**Table 1.** Characteristics of randomized controlled clinical trials included in the analysis of high-grade acneiform rash with combination therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>NCI–CTCAE</th>
<th>Study design</th>
<th>Enrollment number</th>
<th>Sample size</th>
<th>Underlying cancer</th>
<th>Incidence of high-grade acneiform rash (%)</th>
<th>HR for OS</th>
<th>HR for PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butts et al. [25]</td>
<td>II</td>
<td>3</td>
<td>Cetuximab + gemcitabine/ cisplatin or gemcitabine/ carboplatin versus chemotherapy</td>
<td>131</td>
<td>130</td>
<td>NSCLC</td>
<td>14.1</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Rosell et al. [19]</td>
<td>II</td>
<td>2</td>
<td>Cetuximab + cisplatin/ vinorelbine versus chemotherapy</td>
<td>86</td>
<td>85</td>
<td>NSCLC</td>
<td>7.1</td>
<td>0.71</td>
<td>0.71</td>
</tr>
<tr>
<td>Sobrero et al. [28]</td>
<td>III</td>
<td>2</td>
<td>Cetuximab + irinotecan versus irinotecan</td>
<td>1298</td>
<td>1267</td>
<td>CRC</td>
<td>8.2</td>
<td>0.98</td>
<td>0.69</td>
</tr>
<tr>
<td>Tol et al. [17]</td>
<td>III</td>
<td>3</td>
<td>Cetuximab + capecitabine + oxaliplatin + bevacizumab versus capecitabine + oxaliplatin + bevacizumab</td>
<td>755</td>
<td>732</td>
<td>CRC</td>
<td>25.4</td>
<td>1.15</td>
<td>1.22</td>
</tr>
<tr>
<td>Van Cutsem et al. [13]</td>
<td>III</td>
<td>2</td>
<td>Cetuximab + FOLFIRI versus FOLFIRI</td>
<td>1217</td>
<td>1202</td>
<td>CRC</td>
<td>16.2</td>
<td>0.93</td>
<td>0.85</td>
</tr>
<tr>
<td>Pirker et al. [27]</td>
<td>III</td>
<td>2</td>
<td>Cetuximab + cisplatin/ vinorelbine versus chemotherapy</td>
<td>1125</td>
<td>1110</td>
<td>NSCLC</td>
<td>10.4</td>
<td>0.87</td>
<td>0.94</td>
</tr>
<tr>
<td>Lorenzen et al. [20]</td>
<td>II</td>
<td>3</td>
<td>Cetuximab + cisplatin/5-FU versus cisplatin/5-FU</td>
<td>62</td>
<td>62</td>
<td>Esophageal</td>
<td>6.3</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Lynch et al. [26]</td>
<td>III</td>
<td>3</td>
<td>Cetuximab + paclitaxel or docetaxel with carboplatin versus chemotherapy</td>
<td>676</td>
<td>645</td>
<td>NSCLC</td>
<td>10.5</td>
<td>0.89</td>
<td>0.92</td>
</tr>
<tr>
<td>Mitchell et al. [29]</td>
<td>III</td>
<td>N/A</td>
<td>Cetuximab + FOLFOX-4 versus FOLFOX-4</td>
<td>102</td>
<td>100</td>
<td>CRC</td>
<td>18.4</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

NCI–CTCAE, National Cancer Institute—Common Terminology Criteria for Adverse Events; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; NSCLC, non-small-cell lung cancer; N/A, not available; CRC, colorectal cancer; FOLFIRI, irinotecan combined with 5-fluorouracil and leucovorin; 5-FU, 5-fluorouracil.

**Table 2.** Characteristics of clinical trials included in the analysis of high-grade acneiform rash with cetuximab monotherapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Study design</th>
<th>Enrollment number</th>
<th>Sample size</th>
<th>Underlying cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cunningham et al. [12]</td>
<td>II</td>
<td>Cetuximab + irinotecan versus cetuximab</td>
<td>329</td>
<td>115</td>
<td>CRC</td>
</tr>
<tr>
<td>Hanna et al. [34]</td>
<td>II</td>
<td>Cetuximab monotherapy</td>
<td>66</td>
<td>66</td>
<td>NSCLC</td>
</tr>
<tr>
<td>Lenz et al. [32]</td>
<td>II</td>
<td>Cetuximab monotherapy</td>
<td>346</td>
<td>346</td>
<td>CRC</td>
</tr>
<tr>
<td>Saltz et al. [35]</td>
<td>II</td>
<td>Cetuximab monotherapy</td>
<td>61</td>
<td>57</td>
<td>CRC</td>
</tr>
<tr>
<td>Vermorken et al. [10]</td>
<td>II</td>
<td>Cetuximab monotherapy</td>
<td>103</td>
<td>103</td>
<td>SCCHN</td>
</tr>
<tr>
<td>Wierzbicki et al. [30]</td>
<td>II</td>
<td>Cetuximab monotherapy</td>
<td>87</td>
<td>85</td>
<td>CRC</td>
</tr>
</tbody>
</table>

CRC, colorectal cancer; NSCLC, non-small-cell lung cancer; SCCHN, squamous cell carcinoma of the head and neck.
The impact of chemotherapy regimen and line of therapy on development of high-grade acneiform rash

We investigated whether platinum agents have an impact on the incidence of high-grade acneiform rash. The RR in patients receiving a regimen with platinum chemotherapy agent as compared with regimen without was 30.5 (95% CI 13.0–71.4) and 80.4 (95% CI 16.0–402.1), according to the fixed-effects model, respectively (P < 0.001). No difference was observed with and without fluoropyrimidines (RR = 38.1, 95% CI 13.1–110.4 and RR = 37.4, 95% CI 12.9–108.3, respectively; P = 0.98). No statistically significant difference was noted between chemo naive patients receiving first-line therapy, first-line therapy with prior chemotherapy, and second-line therapy (RR = 32.8, 95% CI 9.3–116.1; RR = 42.4, 95% CI 13.4–134.0; RR = 37.4, 95% CI 7.4–188.7, respectively; P = 0.98). Combining patients receiving first-line therapy into one group and comparing with those receiving second-line therapy did not demonstrate any difference (RR = 37.8, 95% CI 16.1–88.4 and RR = 37.4, 95% CI 7.4–188.7, respectively).

Table 3. Summarized incidences and relative risks of acneiform rash with cetuximab and cetuximab in combination with chemotherapy

<table>
<thead>
<tr>
<th>Category</th>
<th>Incidence (95% CI)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All grade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetuximab in combination with chemotherapy</td>
<td>73.1 (68.9–77.0)</td>
<td>11.4 (7.4–17.6)</td>
</tr>
<tr>
<td>High grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetuximab in combination with chemotherapy</td>
<td>12.8 (9.1–17.7)</td>
<td>37.7 (17.8–80.0)</td>
</tr>
<tr>
<td>Cetuximab monotherapy</td>
<td>6.3 (3.7–10.5)</td>
<td>NA</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>15.9 (9.3–25.8)</td>
<td>51.4 (19.2–138.0)</td>
</tr>
<tr>
<td>Non-colorectal cancer</td>
<td>10.5 (8.7–12.5)</td>
<td>24.2 (7.6–77.5)</td>
</tr>
</tbody>
</table>

CI, confidence interval; NA, not available.

Comparison between combination treatment versus monotherapy showed that RR is 2.03 (95% CI 1.52–2.71, P < 0.01). The addition of cytotoxic chemotherapy agents to cetuximab significantly increased the risk of high-grade acneiform rash when compared with cetuximab monotherapy.

Discussion

We demonstrated that patients treated with cetuximab combined with cytotoxic chemotherapy are at high risk of developing acneiform rash. The incidence of all-grade acneiform rash was 73.1% (95% CI 68.9–77.0) for cetuximab in combination with chemotherapy and 12.8% (9.1–17.7) for cetuximab monotherapy. The RR for high-grade acneiform rash was 37.7 (17.8–80.0) for cetuximab in combination with chemotherapy and 37.4 (95% CI 7.4–188.7) for cetuximab monotherapy, respectively. The addition of cytotoxic chemotherapy agents to cetuximab significantly increased the risk of high-grade acneiform rash when compared with cetuximab monotherapy.
Acneiform rash was 73.1% (95% CI 70.7% to 75.5%) with an RR of 11.4 (95% CI 7.4–17.6, P < 0.001) when compared with the control arm. Similarly, patients exposed to a combination treatment are at substantial risk of developing high-grade acneiform rash, the incidence and the RR of which were 12.8% (95% CI 9.1% to 17.7%) and 37.7, respectively (95% CI 17.8–80.0, P < 0.001). The addition of chemotherapy significantly increased the incidence of high-grade acneiform rash when compared with cetuximab monotherapy (RR 2.03, P < 0.01). It should be noted that this was derived from indirect comparison of patients from different trials. This observation has clinical implications since cetuximab in combination with cytotoxic agents has been widely utilized in routine cancer treatments and clinical trials. Its combination with cisplatin and vinorelbine prolongs OS in patients with all histological subtypes of advanced NSCLC [27], and clinical benefit can be achieved regardless of the platinum-based combination [19, 25–27]. Similarly, addition of cetuximab to chemotherapy has shown efficacy in mCRC [12, 13] and SCCHN [37].

The etiology of acneiform rash is not fully elucidated but is attributed to the direct inhibition of the EGFR expressed in undifferentiated proliferating keratinocytes in the basal and suprabasal layers of the epidermis and outer layers of the hair follicle [38]. It leads to premature keratinocyte differentiation, increased attachment, reduced growth and migration, disrupting the formation of a normally protective epidermal barrier. An inflammatory response with increased production of cytokines and recruitment of inflammatory cells also contributes to the development of the characteristic rash [39]. Acneiform rash can be associated with pain and discomfort and negatively impacts patients’ physical, functional and emotional well-being [40, 41]. High-grade reactions result in temporary discontinuation of cetuximab with subsequent dose modifications, potentially diminishing its therapeutic efficacy. A survey conducted among American oncology practitioners revealed that 76% and 32% temporarily interrupted or discontinued therapy with epidermal growth factor receptor inhibitors (EGFRIs) due to rash, respectively [42]. Our findings of a significantly increased risk of high-grade acneiform rash with combination treatment reinforce the need for developing effective management strategies.

Risk factors for developing an acneiform rash have not yet been precisely defined. Younger patients (<70 years) and males undergoing treatment with cetuximab for CRC have been shown to experience a higher rate of grade 3 eruption (6% versus 1% and 7% versus 3%, respectively) [43]. In contrast to our findings, a recent meta-analysis demonstrated that the addition of chemotherapy to erlotinib, a small-molecule tyrosine kinase inhibitor targeting an EGFR, significantly reduced the risk of erlotinib-associated rash [44].

A positive correlation between the presence and severity of cetuximab-induced rash and increased response rates, PFS, and OS has been previously shown [36]. However, KRAS mutation status has also been shown to be an important predictor of mCRC patients’ response. Mutant KRAS status is strongly associated with the lack of response among pretreated chemorefractory patients receiving cetuximab monotherapy or in combination with chemotherapy [45, 46]. In first-line therapy with combination treatment, KRAS mutations in codon 12 or 13 have also been reliably associated with the lack of response, resulting in current recommendation to exclude these patients from anti-EGFR therapy [47]. Future studies will better define eligibility since various KRAS mutations, different codons, and non-activating mutations may be associated with improved outcome [48, 49]. Expression of EGFR has been shown to be a poor predictor of patients’ response [50]. The data on increased EGFR gene copy number are inconsistent, with some studies demonstrating improved outcome with cetuximab first-line therapy and to a lesser extent in pretreated patients [51], while others failing to show its predictive and prognostic value with first-line combination therapy [52]. There are also limited data showing that activating mutations of BRAF confer resistance to anti-EGFR antibodies in ~10% of mCRC patients [46].

The reasons for increased risk of high-grade acneiform rash with combination treatment are unclear. Studies failed to demonstrate pharmacokinetic interactions of cetuximab with irinotecan [53], gemcitabine–carboplatin [54], irinotecan–5-FU–folinic acid [14], 5-FU–folinic acid–irinotecan combinations [55], and irinotecan–5-FU–folinic acid combinations [56].
acid–oxaliplatin [55], and cisplatin–vinorelbine [19], suggesting that this is not a likely explanation. Alternatively, chemotherapy may alter epidermal homeostasis; whether chemotherapeutic agents modify the risk by augmenting an inflammatory response remains to be investigated. In our study, platinum-containing regimens were associated with a reduced risk of high-grade acneiform rash as compared with those without platinum, but this difference was not statistically significant. Neither fluoropyrimidine-containing regimens nor line of chemotherapy modified the risk of high-grade acneiform rash. Overall, however, combination of cytotoxic chemotherapy with cetuximab was associated with increased risk of papulopustular rash.

Our previous meta-analysis of cetuximab monotherapy suggested that the risk of high-grade skin rash may depend on underlying malignancy, with higher incidence of high-grade rash in CRC as compared with non-CRC patients. Our current meta-analysis failed to demonstrate this correlation. Only CRC and NSCLC trials with one trial of esophageal carcinoma were included in the analysis, which may not have had sufficient power to detect a difference. Similarly, in contrast to previous observations, our analysis failed to demonstrate statistically significant correlation between the incidence and severity of acneiform rash and improved PFS and OS, but it may not have been sufficiently powered to detect this difference.

Multiple guidelines for the management of acneiform rash have been proposed but are based on expert opinions and limited data [56–58]. However, two RCTs of prophylactic oral minocycline and doxycycline have been recently conducted [59, 60]. Minocycline 100 mg a day started simultaneously with minocycline and doxycycline have been recently conducted [59, 60]. Minocycline 100 mg a day started simultaneously with minocycline and doxycycline have been recently conducted [59, 60]. Minocycline 100 mg a day started simultaneously with minocycline and doxycycline have been recently conducted [59, 60]. Minocycline 100 mg a day started simultaneously with minocycline and doxycycline have been recently conducted [59, 60].

Topical vitamin K3 analogue, menadione, inhibits phosphatases and it was shown to prevent cetuximab-induced EGFR inhibition and up-regulate phosphorylation of the receptor in in vitro and in vivo experiments [61, 62]. There are currently ongoing phase I and II trials in patients receiving EGFRIs (NCT00656786; NCT01094444). In addition to counseling patients about the skin toxicity before initiation of therapy, active follow-up throughout treatment with timely intervention is recommended to diminish morbidity and optimize the exposure to potentially life-prolonging anticancer therapy.

Our meta-analysis has several limitations. First, the assessment of acneiform rash may vary significantly among investigators and institutions that conducted these trials. The nosology of grading systems used by included trials, NCI–CTCAE v2.0 and 3.0, are not specifically designed to reflect EGFR-associated dermatologic toxic effects, including acneiform rash, and subjective criteria may limit evaluation [63]. Furthermore, the severity may be underreported [64]. Modification of BSA involvement by papulopustular rash (grade 1, <10%; grade 2, 10%–30%; grade 3, >30%) and more specific division of nail toxic effects (e.g. nail loss, ridging, and discoloration) have improved the latest version of CTCAE (v4.0). Impact on instrumental activities of daily living (ADLs) (grade 2) and self-care ADLs (grade 3) has also been added. However, it does not take into consideration the unique distribution of acneiform rash and lacks patient-reported outcome measures. The discrepancies in reporting of dermatologic toxic effects and interobserver differences arising from deficiencies of CTCAE may limit accurate reporting, assessment of patients’ QoL, and accurate interagent comparisons, interfering with our ability to understand the extent and impact of dermatologic toxic effects such as papulopustular rash. Grading systems specific for EGFRI toxic effects such as the Multinational Association for Supportive Care in Cancer EGFR Inhibitor Skin Toxicity Tool may be integrated into the future versions of CTCAE after validation to improve accuracy of reporting [63]. Secondly, meta-analysis is subject to inherent methodological deficiencies of the included trials. The failure of the trials to describe the prevalence of a baseline rash may lead to an overestimation of cetuximab-associated acneiform rash. To minimize the likelihood of bias, we only included RCTs in our primary analysis that directly compared the incidence of acneiform rash in treatment and control arms. Lastly, clinical trials were conducted in major centers and institutes that enrolled patients with adequate organ function and the results may not apply to patient populations with organ dysfunction treated in the community.

conclusions

Our analysis has demonstrated that patients treated with cetuximab in combination with chemotherapy are at significantly increased risk of developing skin toxicity in a form of acneiform rash. More importantly, addition of chemotherapy agents to cetuximab significantly increases the incidence of high-grade acneiform rash as compared with cetuximab monotherapy. With the increased use of combination treatment in patients with advanced solid malignancies, prompt and effective interventions may ameliorate the rash allowing for continued use of cetuximab. In the future, emphasis should be placed on elucidating underlying mechanisms, risk factors and developing effective preventative and management strategies.

acknowledgements

MEL is supported by a Career Development Award from the Dermatology Foundation.

funding

Research Foundation of State University of New York to S.W.; Hana Biosciences and Onyx Pharmaceuticals to M.E.L.

disclosure

MEL has a consultant or advisory role with Bristol-Myers Squibb, ImClone, and received honoraria from Bristol-Myers Squibb, ImClone, YB and XS declare no conflict of interests.


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