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Incidence of cetuximab-related infusion reaction in head and neck cancer patients: may we predict it?

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The combination of cisplatin and fluoruracil with cetuximab is the only regimen showing survival benefit in first-line therapy of relapsed-metastatic head and neck cancer (R-M HNC) in the past 30 years.[1] Similarly, cetuximab is the only target agent significantly improves results of radiotherapy in locally advanced head and neck cancer (L-A HNC).[2]

Cetuximab, a chimeric monoclonal antibody , can induce infusion reactions (IRs) that may be severe and life threatening.[3] In clinical studies, severe IRs are uncommon.[1 2] On the contrary, retrospective studies addressing this matter report higher incidence of severe IR.

We must take into account that patients recruited into clinical studies join strict inclusion criteria and so they might poorly represent the real world population.[4]

In this issue of *ESMO Open*, Coloma *et al*[5] reports a large series of 428 patients treated in the real-world setting with either cetuximab in combination with radiotherapy for L-A HNC, or in combination with chemotherapy for R-M HNC.

The authors showed that 24 (5.4%) patients in this series experienced IR to cetuximab, and they were severe in 23 . This last value was higher than that reported in the Extreme trial 2.7% (chemotherapy+cetuximab)[1] and in the Bonner study 3% (radiotherapy+cetuximab).[2]

Other authors reported high incidence of IR in small retrospective series of patients treated in the real world, as exhaustively reported by Coloma *et al*.[5]

The incidence of severe IR reported in these studies is confirmed by the European Summary of Products characteristics, reporting severe IR in 1%–10% of treated patients[6] and by the Imclone product information, which reports an incidence of 2%–5%.[7]

Interestingly, some findings are similar among all these reports: (A) most IRs occur during the first infusion of cetuximab; (B) the risk of grade 5 toxicity is very low if appropriate premedication and follow-up are carried on; (C) the risk of IR is higher in patients with head and neck cancer (HNC) compared with colon cancer patients; (D) most, but not all, of the studies recorded a relationship between a history of allergy and the development of IR; and (E) some authors observed a relationship between smoking or alcohol consumption and risk of IR, but not all the studies collected information on smoking or alcohol use.

The paper by Coloma *et al* reports the largest retrospective series of patients analysed to point out the incidence and risk factors associated to cetuximab IR.

The observed incidence of IR is in line with other literature data and with the product information published by Merck KGaA and ImClone Systems.

In the univariate analysis, allergy history, alcohol consumption and tobacco history were all significantly associated with the risk of developing IR.

The combination of tobacco and alcohol consumption and allergy history remained significantly associated with severe IR in the multivariate logistic regression models.

No other factors, such as site of primary, previous treatment or lymphocyte/eosinophil counts, correlate with occurrence of IR.

Although most of the previously published analyses report the correlation between alcohol and IR, smoking and IR and history of allergy and IR, this is the first paper showing the correlation among all these variables and IR in the same series. It could be due to the large number of the patients analysed.

The additional value of this paper is the observation that the combination of all these factors correlates with the strongest risk of IR development: 22% of the patients exhibiting all the three risk factors developed severe IR compared with 2.8% of patients with allergy

history alone, 6.7% of patients with alcohol and smoking history and 1% of patients without any of them.

The high incidence of smoking and alcohol history in patients with HNC may easily account for the higher number of IR observed compared with patients with colon cancer.

Although no definitive answer exists about the mechanism linking IR to smoking, alcohol and allergy history, many studies show a relationship between alcohol and smoking history and the risk of developing allergies.[8–10]

The paper of Coloma *et al* is a retrospective analysis and suffers from the limitations of retrospective analyses. However, considering that most studies on this topic move on to the same direction, we should take into account the proposed risk factors in the daily clinical practice.

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