A meta-analysis on the risk of infection associated with intravenous iron therapy in cancer-associated anaemia: a double-edged sword?

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Key Points

- Cancer associated anaemia is a challenging condition with consequences for patients by compromising quality of life and treatment options.
- Our findings on infection risk related to i.v. administration based on our systematic review and meta-analysis, indicates a numerical increase of infections, but it was not statistically significant.
- Inconsistencies in infection reporting stress the necessity for future trials using standardized infection definitions.
- Clinicians should consider the infection risk of i.v. iron against transfusions and/or ESA taking into account the overall risk/benefit ratio. i.v. iron remains an effective treatment with low complications, improving compliance and reducing costs in cancer associated anaemia.

INTRODUCTION

- The prevalence of anaemia in cancer patients varies based on the type of cancer and disease stage, with most studies indicating rates ranging from 30% to 90%

- Cancer-associated anaemia (CAA) is linked to the administration of chemotherapy or the malignancy itself, often compromising therapeutic option and reducing quality of life.

- To treat CAA, iron supplements have been suggested alone or as a complementary treatment alongside ESA.

- 2004, Auerbach et al. [1] provided the first evidence that i.v. iron had a positive impact on enhancing the effectiveness of ESAs in increasing haemoglobin levels with a three-fold benefit in CAA compared to oral iron.

- But, on the other hand, there is evidence that administration of i.v. iron could increase the risk of infection by counteracting the body's protective iron sequestering mechanism. This safety concern is crucial and has not been analysed for the immunosuppressed cancer patients.

METHODS AND MATERIALS

- Search methods: We searched PubMed from January 2004 to July 2023 using the following terms: (Iron OR sodium ferric gluconate OR iron dextran OR Iron-Dextran Complex OR ferric citrate OR Ferric Compounds OR iron-gluconate OR ferrlecit OR iron-gluconate OR feric derisomatose OR Ferrous sulphate OR Monofer OR Venofer OR Injectafer OR oral iron OR parental iron OR intravenous iron OR iv iron) AND (cancer OR hemotherapy or malig nancy or tumor or tumour) AND (Anemia OR can cer-associated anemia OR cancer-induced anemia) AND (randomized controlled trial OR controlled clinical trial)
- Eligibility criteria: We included all randomized controlled phase 3 trials comparing i.v. iron with no-iron or oral iron, with or without ESA for treating CAA. All types of. malignancies were included. Every i.v. iron preparation was included. Only published trials in English were included. Only full articles were included and no abstracts.
- Primary endpoint: The primary endpoint was to assess patients who contracted infectious complications in each study arm during the study period and determine if a statistically significant risk increase existed when administering i.v. iron.

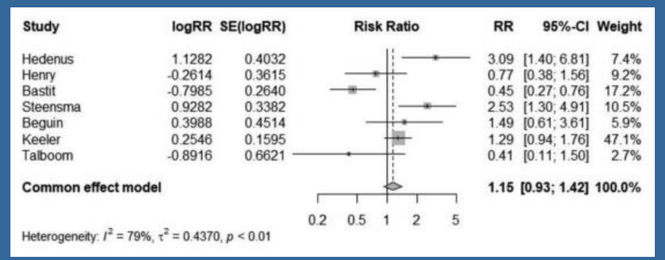
RESULTS

- Through PubMed we identified 1331 results with our research. We identified 18 studies which fulfilled our eligibility criteriawhich have been analysed for documentation of infection. These eighteen studies included 3337 patients. 8 studies documented infectious complications.
- Two studies reported a significant increased risk in infections. One study reported a decreased risk of infectious complications.
- A random effect model was employed. We observed substantial and statistically significant heterogeneity among the risk ratios in the articles. The observed heterogeneity was notably high, with an I2 statistic of 79%, a t 2 value of 0.4370, and a corresponding P-value of <0,01. The pooled risk ratio is equal to 1.15 [0.93; 1.42].

Overview of the study's index

		Number of events/Total			95% Confidence interval		
Author	**Date**	**Treatment**	**Control**	**RR**	**Lower**	**Upper**	**Groups**
Hedenus **[2]**	2007	18/33	6/34	3.09	1.40	6.81	IV VS No iron
Henry **[3]**	2007	9/63	23/124	0.77	0.38	1.56	IV VS oral iron
Bastit **[4]**	2008	18/200	39/196	0.45	0.27	0.76	IV VS No iron
Steensma **[5]**	2011	28/164	11/163	2.53	1.30	4.91	IV VS oral iron
Beguin **[6]**	2013	10/50	7/52	1.49	0.62	3.61	IV VS No iron
Keeler **[7]**	2017	36/55	31/61	1.29	0.94	1.76	IV VS oral iron
Talboom **[8]**	2023	3/96	8/106	0.41	0.11	1.50	IV VS oral iron

Overview of the study's index, including the articles that have been examined in the meta-analysis evaluating the risk of infection in the intravenous iron group compared to the control group.
The 95% confidence interval was computed for the RR (lower and upper bounds).
'RR' corresponds to the Risk Ratio.



DISCUSSION

- In this review, i.v. iron administration was associated in two studies with an increased risk of infection, but this could not be confirmed in the other studies reviewed here.
- Our meta-analysis showed a numerical higher risk in the i.v. iron group but it was not statistically significant.
- Our meta-analysis is subject to limitations mainly stemming from methodological differences and variations in infection reporting. Due to these methodological issues, the best way to address the question of i.v. iron related infections, in the future, would be to design studies powered to determine if there is an increased risk of infection in well defined settings.
- Given those inconsistencies, it is difficult to make a clear conclusion, on the basis of our review.

CONCLUSIONS

- The potential infectious risk of i.v. iron therapy should be balanced against the risk of complications associated with RBC transfusion and the risk/benefit ratio from i.v. iron compared to ESA therapy.
- It would appear sensible not to administer i.v. iron during acute infection, but otherwise, it remains an effective treatment with a low risk of complication for CAA.

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