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# Potential Health Economic Impact of Intravenous Iron Supplementation to Erythropoiesis-Stimulating Agent Treatment in Patients with Cancer- or Chemotherapy-Induced Anemia

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## Key Words

Chemotherapy-induced anemia · Iron deficiency · Iron supplementation

## Abstract

**Background:** Intravenous (i.v.) iron supplementation significantly improves the response to erythropoiesis-stimulating agent (ESA)-based therapies in patients with cancer- or chemotherapy-induced anemia. The economic implications of adding i.v. iron to ESA treatment are less well investigated. Published randomized controlled trials do not provide sufficient data for a comprehensive cost-effectiveness analysis. **Methods:** Preliminary cost calculations from the Swiss health care system perspective based on a meta-analysis and published results of eight randomized controlled trials without correction for decreased ESA need provide a conservative cost-effectiveness estimate. **Results:** The additional total cost of i.v. iron supplementation ranged from EUR 417 to EUR 901 per patient depending on the evaluated iron-carbohydrate complex. Considering a 24% absolute increase in the proportion of ESA responders, the incremental cost-effectiveness ratios per additional responder are EUR 1,704–3,686. In routine practice, better values may be achieved due to ESA dose savings. **Conclusion:** Supplementation of ESAs with i.v.

iron appears to be an economically viable treatment option in anemic cancer patients. Additional research on ESA dose savings and cost-effectiveness is required.

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## Background

Anemia is a common condition in cancer patients, especially when receiving chemotherapy [1]. It substantially increases treatment costs [2, 3] and affects the quality of life [4]. Health state utility scores of 0.48–0.56 for subjects with severe anemia compare to scores of patients with metastatic disease [5, 6].

Erythropoiesis-stimulating agents (ESAs) are an approved treatment option in anemic cancer patients receiving chemotherapy [7, 8]; however, ESA costs are high and a health technology assessment estimated incremental cost-effectiveness ratios (ICERs) of GBP 40,000–150,000 per quality-adjusted life year gained [5]. Furthermore, safety concerns limit their use [8]. Thus, the EMA indicates a need for caution [9] and the US FDA requires a Risk Evaluation and Mitigation Strategy (REMS) [10].

Optimization of iron stores with intravenous (i.v.) iron supplementation of ESA therapy significantly improved

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**Table 1.** Assumed input parameters based on the official Swiss tariff list (TARMED)

	TARMED reference No.	EUR <sup>a</sup>
Consultation first 5 min	00.0010	12.29
Consultation next 5 min (max 2 ×)	00.0020	12.29
Consultation last 5 min	00.0030	12.29
Small clinical examination (e.g. height, weight)	00.0410	39.24
Injection/infusion by nonmedical staff	00.0750	5.67
Cost of administration of i.v. iron		
Push i.v. injection	00.0010 + 00.0030 + 00.0750	30.24
Slow i.v. injection (2 min)	00.0010 + 00.0030 + 00.0750	30.24
Slow i.v. injection (15 min)	00.0010 + 00.0020 + 00.0030 + 00.0750	42.53
i.v. infusion (<1 h)	00.0010 + 2 × 00.0020 + 00.0030 + 00.0750	54.82
i.v. infusion per hour (pro rata temporis)	Hosp	35.89
Hospitalization (1 day)	Hosp	861.32
If a test dose injection is needed, add	00.0410	39.24

<sup>a</sup> One TARMED point is reimbursed with EUR 0.69.

the hemoglobin response in patients with cancer- or chemotherapy-induced anemia (CIA) [11–18]. However, little is known about the economic implications of adding i.v. iron to ESAs in this indication.

We report a preliminary economic assessment of i.v. iron supplementation in ESA-treated anemic cancer patients from the Swiss health care perspective.

## Methods

A systematic review and meta-analysis of studies on i.v. iron supplementation of ESAs in patients with CIA was used as a basis for this study [19]. The meta-analysis included eight studies on i.v. iron versus no or oral iron supplementation that were reported until 2010 (hematopoietic response defined as an increase in hemoglobin of >2 g/dl or above 12 g/dl) [19]. Information on response rates was retrieved from the meta-analysis, and dosages of i.v. iron and ESAs were taken from published results of the individual studies [11–14, 16–18, 20] and pooled and weighted according to study size.

Equal efficacy of different i.v. iron preparations was assumed. In absence of data on actual ESA dose adjustment, our conservative cost model also assumed that the initial ESA dosage would be maintained over the entire treatment period.

Drug treatment costs were assessed from the perspective of the Swiss health care system. The ESA cost per patient was based on the publicly reimbursed price of relevant ESA preparations [proportional use in Switzerland: epoetin alfa 9%, epoetin beta 35%, darbepoetin alfa 56% (IMS Midas 2010-Q1)]. Costs of ferric gluconate (FG; EUR 11.39), iron dextran (EUR 20.51), iron sucrose (EUR 22.78), and ferric carboxymaltose (FCM; EUR 27.84) were based on the publicly reimbursed price per 100 mg iron. Since iron dextran and FG are not available on the Swiss market, prices were

assumed to be 10 and 50% lower than the price of iron sucrose (based on experience with other markets and the Swiss pricing system), respectively. Administration costs of different i.v. iron preparations were derived from the official Swiss tariff list (table 1; <http://onb.tarmedsuisse.ch/>) [21].

Cost implications and ICERs were estimated relative to the reference case of no i.v. iron use. Drug and administration costs are valid for the year 2011 and are shown in euros (1 EUR = 1.273 CHF, May 2011).

## Results

Eight relevant randomized controlled trials of i.v. iron-supplemented ESA treatment included 1,555 anemic cancer patients. The weighted mean proportion of responders to ESA therapy was 84% in the i.v. iron arms compared to 60% in the reference arms (+24%). On average, 1,191 mg i.v. iron were administered over a mean observation period of 13.97 weeks. Mean i.v. iron doses ranged from 600 to 2,000 mg and were generally well tolerated. Apart from one study [11], all trials adjusted ESA doses depending on hemoglobin values, but only one [16] reported total ESA doses.

The ESA cost per patient during the observation period was EUR 8,196. The additional total cost per patient of i.v. iron supplementation ranged from EUR 417 (FCM) to EUR 901 (FG) including estimated administration costs of EUR 85 (FCM) and EUR 766 (FG), respectively (estimates for 1,191 mg). The 24% increment in hemoglobin response with i.v. iron versus no or oral iron supple-

**Table 2.** Treatment regimen and i.v. administration costs of 1,000 mg iron over a 10-week treatment period based on SmPC and the Swiss tariff list (TARMED)

	FG	Iron dextran	Iron sucrose	FCM
Treatment regimen				
Maximum approved dose per administration	62.5 mg in 10 min	100 mg in 2 min 1,000 mg in 7 h	200 mg in 10 min 500 mg in 3.5 h	200 mg push i.v. 1,000 mg in 15 min <sup>a</sup>
Cost of administration				
Administration scheme	62.5 mg in 10 min	1,000 mg in 7 h	500 mg in 3.5 h	500 mg in 15 min <sup>b</sup>
Sessions needed (excluding loading dose), n	16	1	2	2
Cost of test dose, EUR	0	37	0	0
Administration cost, EUR	680	290	251	85
Drug cost, EUR	114	205	228	278
Total cost of administration, EUR/1,000 mg iron	794	495	479	363

SmPC = Summary of Product Characteristics.

<sup>a</sup> Maximum 15 mg/kg body weight.

<sup>b</sup> The analysis assumed two 500-mg injections, which represents the administration scheme of current clinical practice.

mentation corresponded to ICERs of EUR 1,704, EUR 2,187, EUR 2,455, and EUR 3,686 per additional responder for FCM, iron dextran, iron sucrose, and FG, respectively.

## Discussion

A recent meta-analysis of randomized controlled clinical trials on i.v. iron supplementation of ESA therapy in anemic cancer patients summarized the improved hematologic response versus no or oral iron supplementation [19]. However, published data do not include i.v. iron-associated ESA dose reduction. Therefore, our calculations are based on a conservative approach assuming a constant ESA dosage over the treatment period. However, in routine practice, ESA administration would likely be delayed or reduced upon hematologic response to i.v. iron supplementation. In anemic patients with lymphoid malignancies who did not receive chemotherapy, a 25% reduction of weekly mean ESA dosages at the end of a 16-week treatment period and overall cost savings of 11% over the entire treatment period were reported [16, 22].

Under our conservative assumption, the addition of i.v. iron to ESA treatment of CIA patients would lead to a cost of EUR 1,704–3,686 per additional responder to ESA treatment. Given the use of the ‘metric’ of additional responders in the denominator of the cost effectiveness equation (representing clinical effectiveness in the

absence of alternatives), this result needs the following discussion. A more comprehensive assessment of the cost-effectiveness of i.v. iron supplementation would require data on associated ESA dose reductions. Notably, a former cost analysis based on a single study in 60 patients with CIA estimated savings of USD 1,300 per i.v. iron-supplemented patient [23]. In addition, blood transfusion requirements may be reduced upon i.v. iron administration to anemic cancer patients [13, 19, 24, 25] and further increase the cost benefit of i.v. iron. However, given insufficient data on the use of blood transfusions, we did not consider this aspect in our calculations. Clinical studies of i.v. iron at recommended doses [26] did not show unexpected AEs [11–14, 16–18, 20, 27]. Long-term studies are warranted, yet preliminary data on i.v. iron supplementation of ESA-treated patients showed no effect on 3-year progression-free survival [14, 28]. Costs of management of potential AEs were not included in our analysis. The economic results presented here reflect the perspective of the Swiss health care system as a mainly third party payer-funded health care system. The results may be indicative for markets with similar health care systems, although the underlying health economic models will need adjustment before they can be applied to other countries. The model may also need some adaption when biosimilars of ESAs become available at reduced costs.

The main cost factors of i.v. iron administration are the number and duration of required infusions (table 2). Accordingly, lowest total administration costs per 1,000

mg iron were estimated for FCM (assuming 2 infusions of 500 mg iron each). FCM is a dextran-free i.v. iron preparation that allows rapid administration of up to 1,000 mg iron without need for a test dose. Therefore, FCM showed a favorable cost profile although direct drug costs for this substance were higher than for the other i.v. iron preparations. This result requires verification under routine practice conditions.

Given the clinical advantages of i.v. iron supplementation and a potential yet unproven economic benefit, further studies on the potential of i.v. iron to reduce ESA-related cost in routine treatment of anemic cancer patients are warranted.

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## Disclosure Statement

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