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Discussant
M. DICATO
Hematology-Oncology
Centre Hospitalier de Luxembourg
L- L- 1210 Luxembourg

Reduction in nephrotoxicities using short hydration in chemotherapy containing cisplatin:

a consecutive analysis of 467 patients with thoracic malignancies

Midori Tanaka, Hidehito Horinouchi, Hideaki Shiraishi, Kenjiro Tsuruoka, Kazushi Yoshida, Kota Itahashi, Tetsuhiko Asao, Shinsuke Kitahara, Yasushi Goto, Shintaro Kanda, Yutaka Fujiwara, Hiroshi Nokihara, Noboru Yamamoto, Yuichiro Ohe

Department of thoracic oncology, National Cancer Center Hospital, Tokyo, Japan

Background

- Cisplatin plays a crucial role in cytotoxic chemotherapy for patients with solid tumors including lung cancer. Management of gastrointestinal and renal toxicities have been an important issue concerning this agent. Based on early phase trials in the 1980's, continuous and high-volume hydration have been recommended for patients who receive cisplatin.
- Novel antiemetics such as 5-HT_3 receptor and neurokinin-1 (NK-1) receptor antagonist dramatically improved the management of gastrointestinal toxicities associated with cisplatin.
- Recently, increasing number of clinical trials have demonstrated the feasibility of short and lower volume hydration (short hydration) for patients in whom cisplatin had been indicated. However, research comparing conventional and short hydration in cisplatin administration is very sparse.
- We conducted a retrospective study to evaluate the difference of frequency and severity of nephrotoxicity between short hydration and conventional hydration in patients with thoracic malignancy treated using cisplatin.

Patients and Methods

- We conducted a consecutive retrospective analysis of patients with thoracic malignancies who had been treated with chemotherapy including CDDP at a dose of ≥60 mg/m^2.
- All the patients received aprepitant, an 5-HT$_3$ blocker and dexamethasone based on the guidelines about gastrointestinal toxicities.
- Eligible patients were between 20 and 69 years of age.
- Patients who had enrolled in clinical trials were excluded.
- Examples of short and conventional hydration (pemetrexed plus CDDP) are shown in Figure 1.
- Logistic regression analysis was conducted to assess the impact of multiple clinical factors upon the abnormal creatinine value after the first cycle of CDDP. The predictive factors included were as follows; age, sex, ECOG performance status (PS), concomitant thoracic radiotherapy, the dose of CDDP, degree of gastrointestinal adverse events, Mg supplementation, baseline creatinine (Cr) values and the method of hydration.

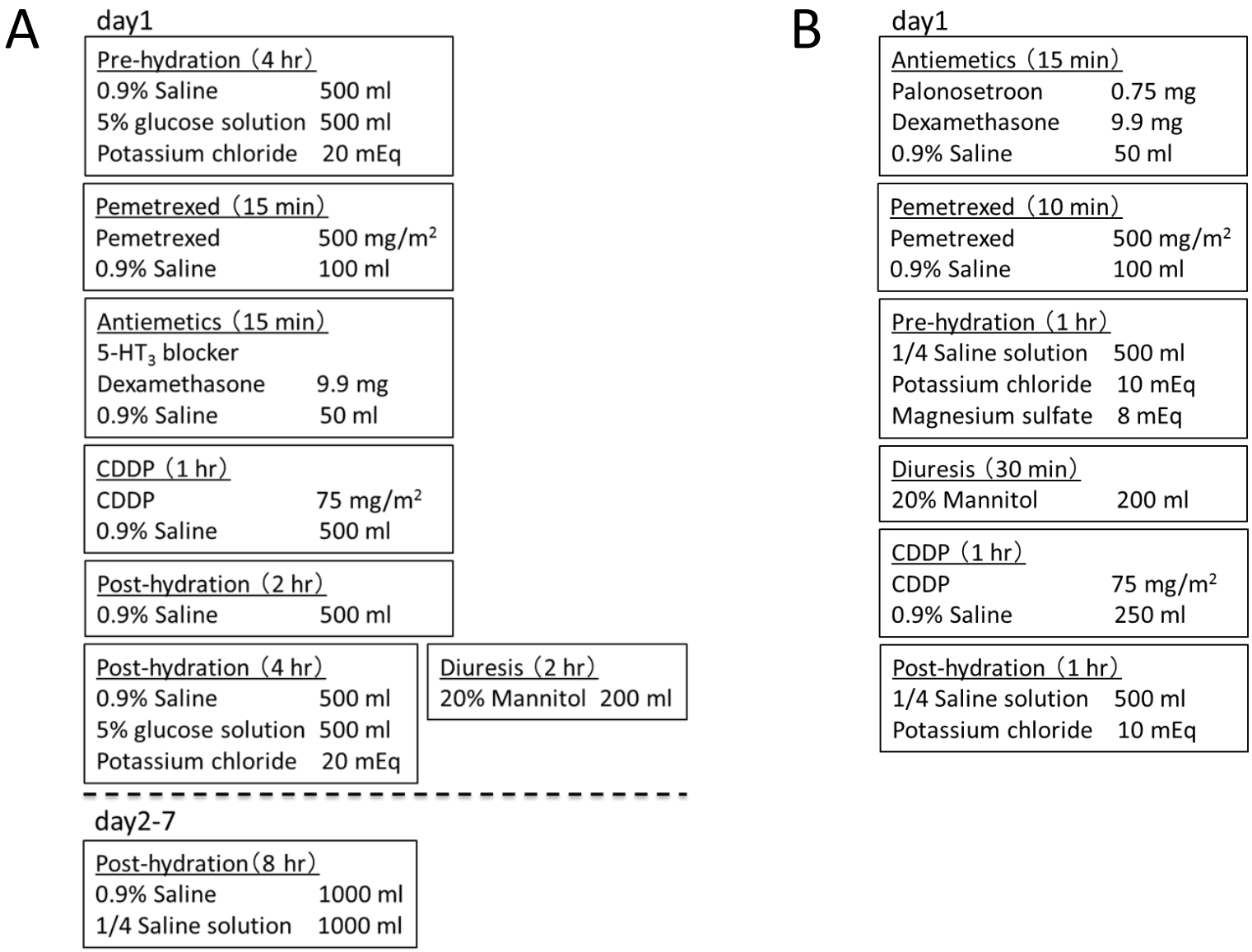


Figure1. An example of the chemotherapy regimen.
（A）Convensional hydration,（B）Short hydration

Renal function after chemotherapy

After first cycle

	Conventional		Short	
	n=356	% or range	n=111	% or range
Cr elevation (%)				
G 0	308	86.5	107	96.4
G 1	45	12.6	4	3.6
G 2 *	3	0.9	0	0
Serum Cr (mg/dl)				
Median (range)	0.76	0.37-2.5	0.75	0.4-1.3
Estimated Cr clearance*1 (median)	83.6	30.3-240.6	87.2	42.9-153.2
Calculated eGFR*2 (median)	76.0	22.2-167.4	77.5	44.1-141.7

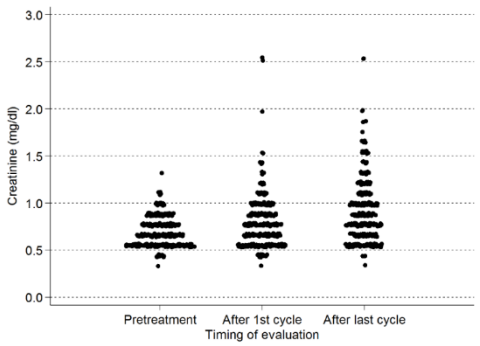
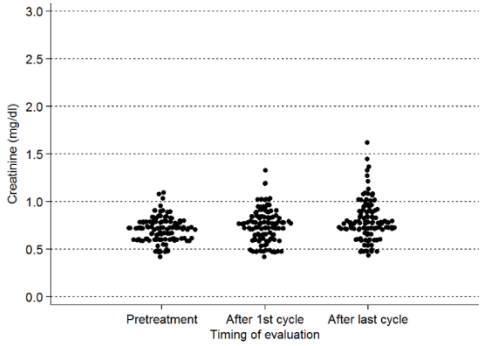
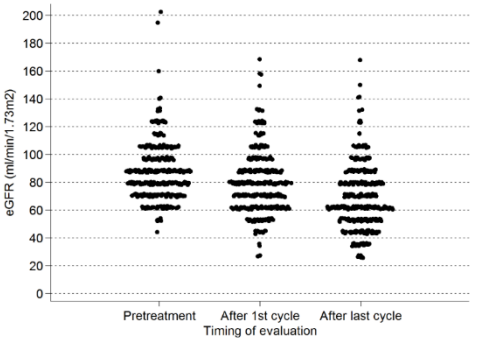
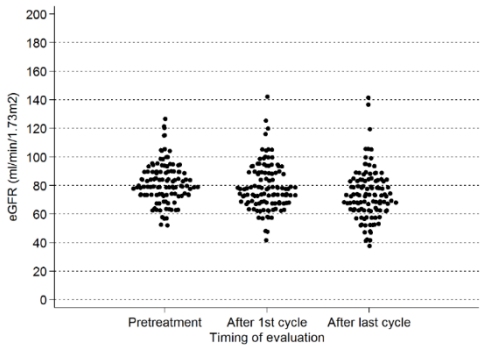
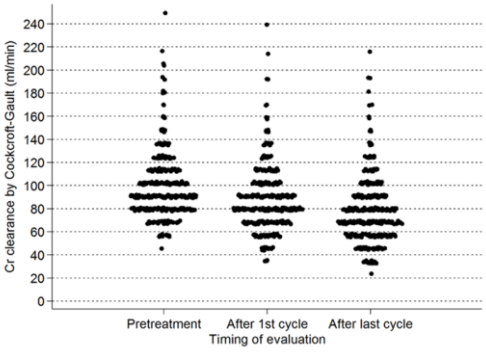
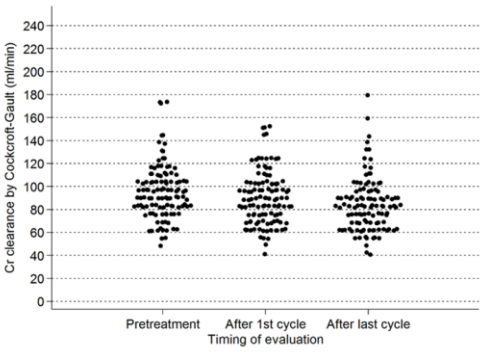
After last cycle

	Conventional		Short	
	n=356	% or range	n=111	% or range
Cr elevation (%)				
G 0	238	66.9	95	85.6
G 1	103	28.9	16	14.4
G 2	15	4.2	0	0
Serum Cr (mg/dl)				
Median (range)	0.80	0.37-2.5	0.79	0.4-1.6
Estimated Cr clearance*1 (median)	73.2	27.0-216.9	82.1	38.1-176.1
Calculated eGFR*2 (median)	65.3	22.2-167.4	73.7	36.9-141.7

*1 Calculated Cr clearance by the Cockcroft-Gault equation, ml/min

*2 Estimated glomerular filtration rate by the Japanese equations for estimating glomerular filtration rate from serum Cr, ml/min/1.73m^2

Sequential evaluation of renal function

	Conventional hydration	Short hydration
Creatinine value		
eGFR		
Cr clearance		

Factors associated with abnormal Cr

Evaluation of predictive factor for abnormal creatinine value*1 after first cycle of cisplatin based chemotherapy (logistic regression analysis)

	Univariate		Multivariate	
	OR (95% C.I.)	p value	OR (95% C.I.)	p value
Age (yr) <62 vs. ≥62	1.43 (0.79-2.57)	0.234	1.70 (0.89-3.26)	0.109
Sex Female vs. Male	1.00 (0.54-1.87)	0.991	1.27 (0.61-2.63)	0.528
PS 0-1 vs. 2-3	0.72 (0.09-5.69)	0.756	1.04 (0.12-8.78)	0.968
Chemoradiotherapy No vs. Yes	2.34 (1.30-4.23)	0.005	2.50 (1.26-4.96)	0.009
Cisplatin dosage 60 mg/m² vs. 75 or 80 mg/m²	1.95 (0.68-5.61)	0.216	2.03 (0.60-6.87)	0.255
Highest GI Adverse event*2 0-1 vs. 2 or higher	1.76 (0.85-3.62)	0.127	2.02 (0.89-4.59)	0.091
Mg supplementation No vs. Yes	1.91 (0.93-3.96)	0.080	1.63 (0.73-3.65)	0.230
Baseline creatinine value Normal vs. Abnormal*1	16.2 (5.62-46.9)	<0.001	30.5 (8.87-104)	<0.001
Method of hydration Conventional*3 vs. Short hydration	0.24 (0.08-0.68)	0.007	0.19 (0.06-0.61)	0.006

*1 Creatinine value higher than the upper limit of creatinine value.
*2 Highest gastrointestinal adverse event including anorexia, nausea and vomiting evaluated by CTCAE ver 4.0.
*3 Conventional method of hydration with a longer time of administration and higher volume of fluid infusion.

Cisplatin: Short Hydration

- Vogl S et al. Cancer1980

Cisplatin in a 2h outpatient regimen with diuresis and hydration:

Saline furosemide and mannitol

Créatinine > 2mg/dl in 3/158 patients

2 cases of hearing loss!

- Brock J et al : Cancer Treat. Rep 1986

50-120mg of Cisplatin added to 400 ml of 10% mannitol to 1l with saline + $MgSO_4$ given iv/1h followed by 1l of saline/1h

Decrease in CrCl from course 1 to 6:

4,9% for 50-60mg/m2 of CDDP

13,9% for 70-90mg/m2 of CDDP

14,9% for 100-120mg/m2 of CDDP

JJCO Japanese Journal of Clinical Oncology

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Short Hydration in Chemotherapy Containing Cisplatin (≥75 mg/m^2) for Patients with Lung Cancer: A Prospective Study

Hidehito Horinouchi*, Kaoru Kubota, Hidetoshi Itani, Tomoko Katsui Taniyama, Shinji Nakamichi, Hiroshi Wakui, Shintaro Kanda, Hiroshi Nokihara, Noboru Yamamoto, Ikuo Sekine and Tomohide Tamura

Division of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan

*For reprints and all correspondence: Hidehito Horinouchi, Division of Thoracic Oncology, National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-ku, Tokyo 104-0045, Japan. E-mail: hhorinou@ncc.go.jp

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Lung Cancer patients treatment: =/> 75 mg/m2 of CDDP
N=44pts, median age 64y., 20/44 pts: CDDP + pemetrexed

Hydration regimen:
500ml +10 mEq of KCl/60 minute period pre- and post CDDP, 20% mannitol 200ml as forced diuresis/30 minutes. 8 mEq MgSO4 added to prehydration.
Median duration 4h (3,3- 6,8), median volume: 1600 ml (1550- 2050).

43/44 patients: no problem. 1/44 patient had a transient increase of creatinine to 1,7 mg/dl. Completed his planned program

Conclusion: short hydration is safe for CDDP =/> 75mg/m2 in pts with lung cancer

Conclusions

- **Retrospective non randomized study**
- After the first cycle, the proportion of grade 2 or more Cr increase was 0% in patients who received short hydration, compared with 0.9% in the conventional hydration group. After the last cycle of CDDP, the incidence of grade 2 or more Cr increase was still 0% in patients who received short hydration, compared with 4.2% in patients who received conventional hydration.
- Patients using short hydration for CDDP administration experienced a significantly lower frequency of abnormal creatinine values after the first cycle.
- To reduce nephrotoxicity in CDDP-containing regimens, short hydration (should) **if validated by a confirmatory study, could** be recommended in patients with thoracic malignancies.

(underlined and colored text by discussant!)

Real-life efficacy of an epoetin alfa biosimilar in chemotherapy-induced anemia: The SYNERGY study

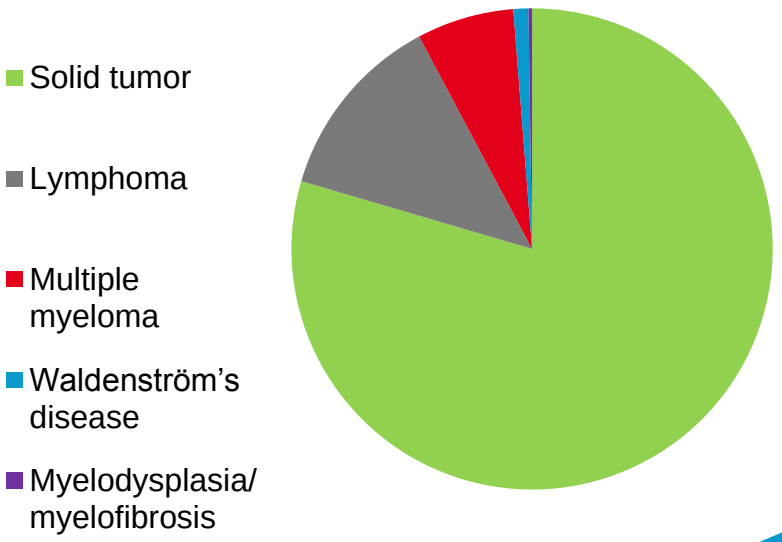
F Scotté, K Laribi, C Gisselbrecht, D Spaeth, E Kasdaghli, E Leutenegger, I Ray-Coquard, H Albrand

Poster 373PD
Presented at ESMO Asia 2015, Singapore, 18–21 December 2015.

SYNERGY: How do clinicians use epoetin zeta and iron to treat CIA in practice?

Patients

- Mean age 67 years old
  - Approx 50% ≥70 years old
- ECOG PS of 0 or 1 in 75.7%



Epoetin zeta

- SC administration (99.2%)
- Once-weekly injection (98.6%)
- 20,000–40,000 IU dose (97.7%)
- Median duration 11.0 weeks (range 0.1–29.7)

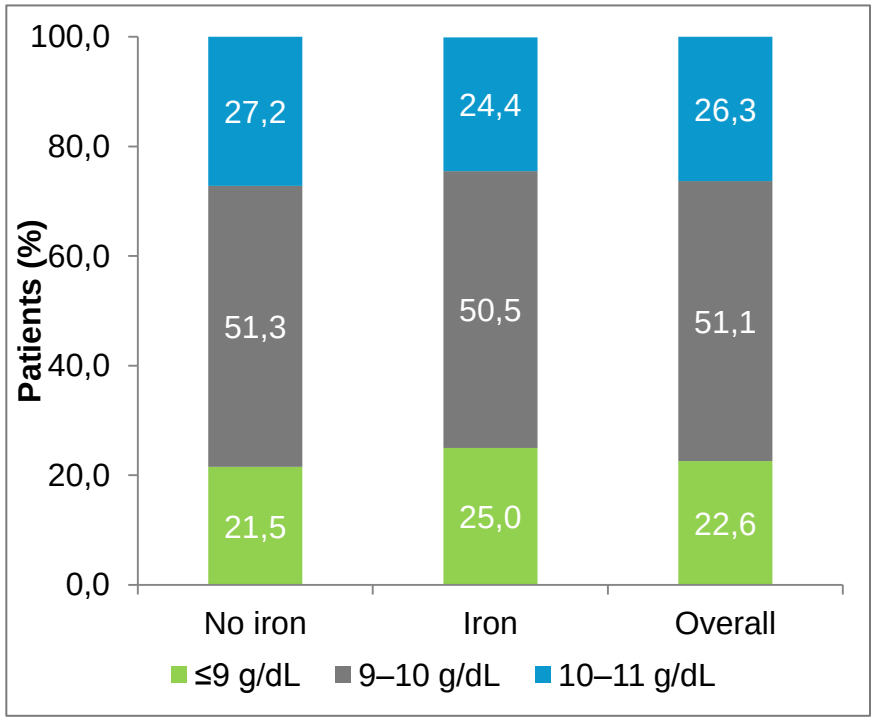
Iron supplementation

- Concomitant with epoetin zeta in 31.6%
  - IV in 58.9%
  - Oral in 40.5%

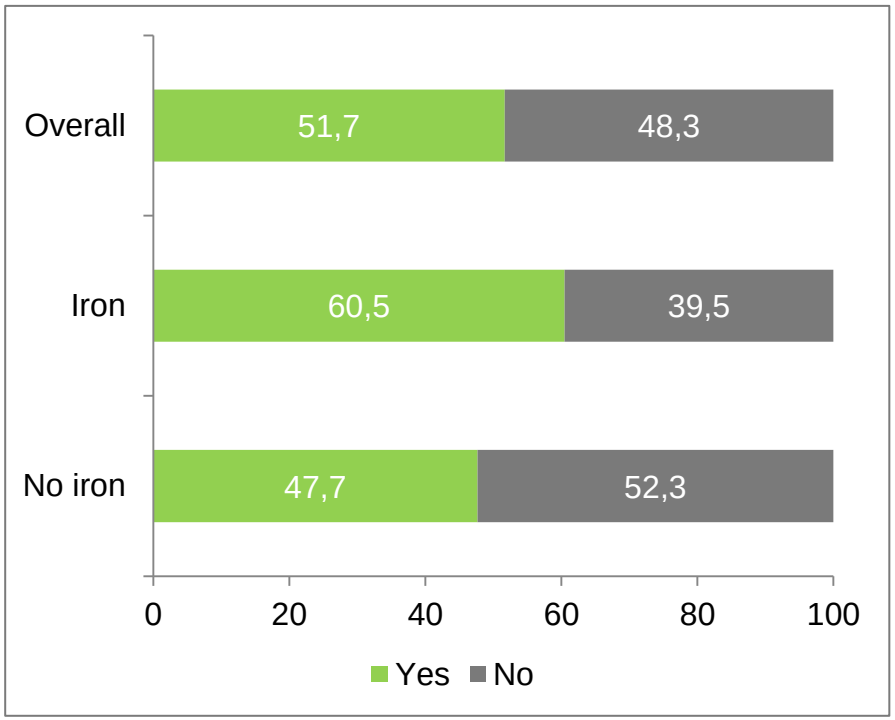
CIA, chemotherapy-induced anemia; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IV, intravenous; SC, subcutaneous

Monitoring of anemia and iron status

Hb level in baseline population



Iron status assessment



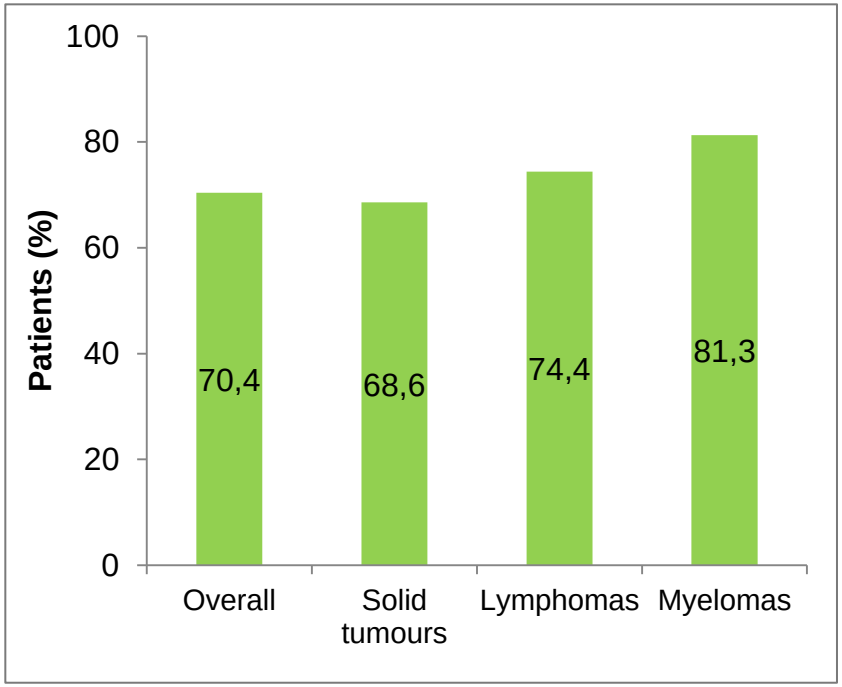
- Most patients had mild–moderate anemia
- Patients prescribed iron were more likely to have had an iron assessment
- More patients had an iron assessment than in previous French cohorts[1,2]

Hb, hemoglobin

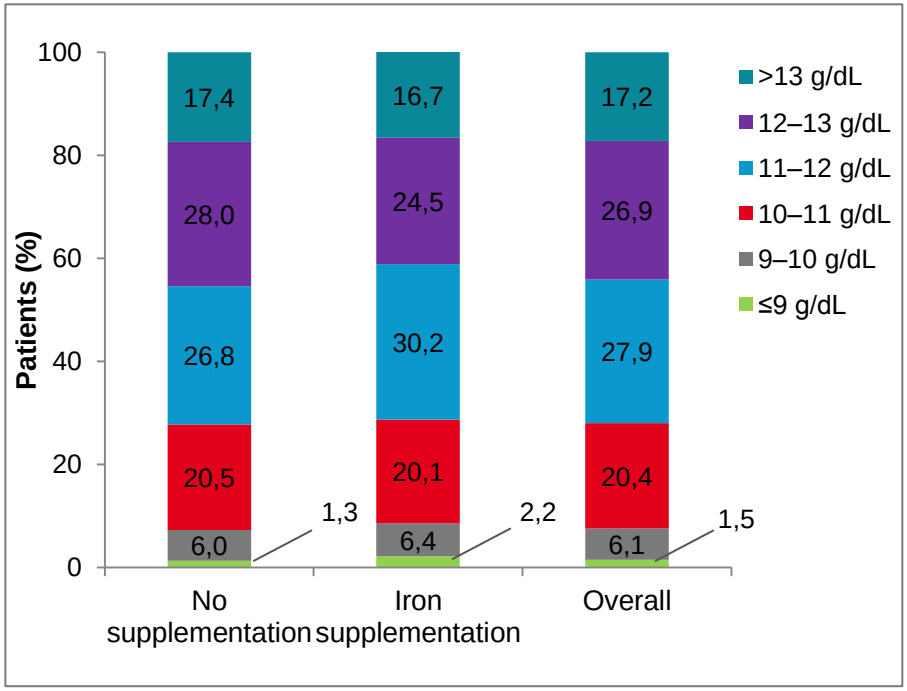
1. Ludwig H et al. *Support Care Cancer* 2014;22:2197–2206; 2. Spielmann M et al. *Eur J Cancer* 2012;48:101–107

Epoetin zeta is effective and well tolerated

Response* to epoetin zeta treatment



Maximum Hb level achieved on study



- Iron supplementation did not affect the response to epoetin zeta in these patients
- AEs occurred in 3.4% of patients; 2.0% were thromboembolic events

*Defined as target Hb level reached with an increase of ≥1 g/dL from baseline or an increase of ≥2 g/dL in the absence of transfusion in the previous 3 weeks, or if treatment discontinued due to Hb remaining above target for 3 weeks without transfusion

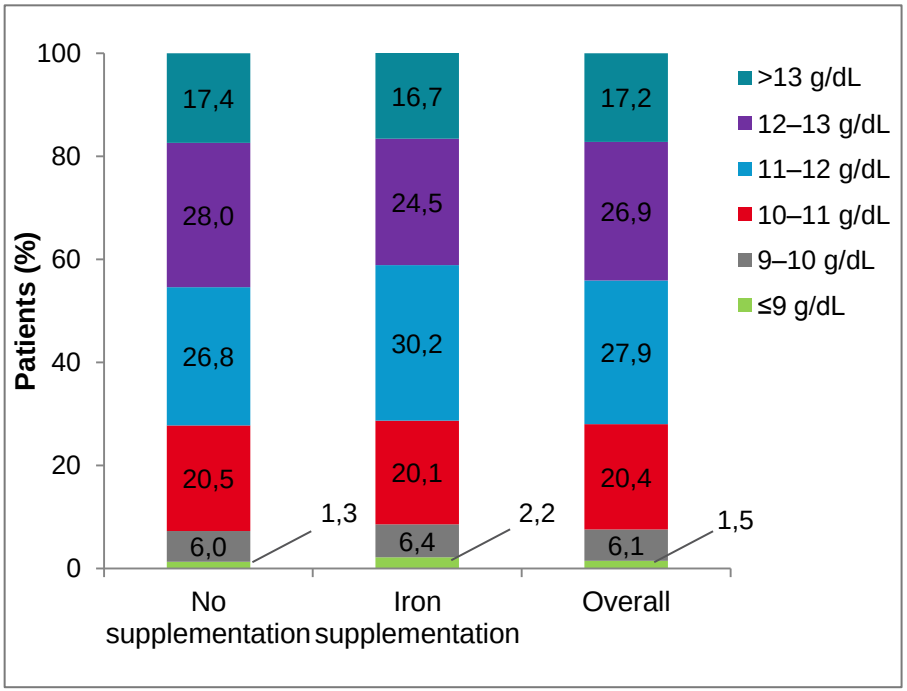
AEs, adverse events; Hb, hemoglobin

Table 2. Anaemia and monitoring of iron status in the baseline population (N=2076)

Characteristic	No supplementation (n=1421)	Iron supplementation (n=655)	Analysed population (n=2076)
Hb, n (%)			
≤9 g/dL	305 (21.5)	164 (25.0)	469 (22.6)
9–10 g/dL	729 (51.3)	331 (50.5)	1060 (51.1)
10–11 g/dL	387 (27.2)	160 (24.4)	547 (26.3)
Severity of anaemia, Hb g/dL, n (%)			
Normal (≥11.0)	3 (0.2)	2 (0.3)	5 (0.2)
Mild (9.5–11.0)	891 (62.7)	379 (57.9)	1270 (61.2)
Moderate (8.0–9.5)	503 (35.4)	270 (41.2)	773 (37.2)
Severe (6.5–8.0)	22 (1.5)	3 (0.5)	25 (1.2)
Very severe (<6.5)	2 (0.1)	1 (0.2)	3 (0.1)
Iron status assessment, n (%)			
No	743 (52.3)	259 (39.5)	1002 (48.3)
Yes	678 (47.7)	396 (60.5)	1074 (51.7)
Patients with data available, n (%), for			
Serum iron	596 (41.9)	364 (55.6)	960 (46.2)
Ferritin	623 (43.8)	352 (53.7)	975 (47.0)
TSAT	563 (39.6)	351 (53.6)	914 (44.0)
Recent iron assessment* (mean±SD)			
Serum iron, µg/100 mL	63.7±60.3	34.4±44.0	52.5±56.4
Ferritin, µg/L	569.5±639.5	557.2±594.2	565.0±623.1
TSAT, %	29.5±19.1	17.3±12.7	24.8±17.9

Hb levels:

Maximum Hb level achieved on study



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AEs, adverse events; Hb, hemoglobin

Summary

- Observational longitudinal prospective multicenter study in France
- Solid tumors, lymphomas, myelomas. No leukemia in study.
- Primary objective: study the impact of a biosimilar ESA in chemotherapy induced anemia and the response rate +/- iron added to ESA
- N=2167, on study 2076
- Supplemental Fe given n= 655, iv 58,9%, p.o. 40,5%
- Fe assessment 51,7%, of which 60,5% were given iron.

Comments

- Large study
- Iron did not affect response: Iron status to be correlated in an individual patient based manner
- Transferrin saturation data not optimal
- ? Difference of response to iv or p.o iron?
- Correlation of therapy given to group of patients > 12g of Hb representing: 45% of all study patients, and 17% of all study patients > 13g
- Additional data to be retrieved: individual patient data to link dose of ESA, iron given, if so iv or p.o., dose
- Improvement of iron management compared to previous study in France: 2012 Spielmann, Eur J. Cancer: 19%, now ~51%.