available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Short Communication

Managing cancer-related anaemia in congruence with the EORTC guidelines is an independent predictor of haemoglobin outcome: Initial evidence from the RESPOND study

Matti Aapro[a], *Joanna Van Erps*[b], *Karen MacDonald*[c], *Pierre Soubeyran*[d,e], *Michael Muenzberg*[f], *Matthew Turner*[f], *Hans Warrinnier*[g], *Tara Albrecht*[c,h], *Ivo Abraham*[c,i,*]

[a]*Institut Multidisciplinaire d'Oncologie, Clinique de Genolier, 1 Route du Muids, CH-1272 Genolier, Switzerland*
[b]*Afdeling Oncologie en Hematologie, Algemeen Stedelijk Ziekenhuis Aalst, Merestraat 80, B-9300 Aalst, Belgium*
[c]*Matrix45, 620 Frays Ridge Road, Earlysville, VA 22936, USA*
[d]*Institut Bergonié, 229 cours de l'Argonne, F-33076 Bordeaux, France*
[e]*Université Victor Segalen Bordeaux 2, 146 rue Léo Saignat, F-33076 Bordeaux, France*
[f]*F. Hoffmann-La Roche AG, Grenzacherstrasse, Bau 74, CH-4070 Basel, Switzerland*
[g]*Roche, Dantestraat 75, B-1070 Brussel, Belgium*
[h]*School of Nursing, University of Virginia, 202 15th Street SW, Charlottesville, VA 22903, USA*
[i]*College of Nursing and Center for Health Outcomes and Pharmacoeconomic Research, Department of Pharmacy Practice and Science, College of Pharmacy, University of Arizona, 1305 N. Martin Road, Tucson, AZ 85721, USA*

ARTICLE INFO

Article history:
Received 22 June 2008
Received in revised form
5 September 2008
Accepted 30 September 2008
Available online 6 December 2008

Keywords:
Anaemia
Evidence-based practice guidelines
Erythropoietin

ABSTRACT

Purpose: To model the relationship between scores for practicing in congruence (CSs; 0–10) with EORTC guidelines for erythropoietic proteins (EPs) and haemoglobin (Hb) outcomes observed in the validation study of the RESPOND system.

Methods: Thirty four patient pairs matched on cancer type and chemotherapy in pre- (retrospective; clinicians not using RESPOND) and post-cohorts (prospective; clinicians using RESPOND) followed over 4 months following EP treatment initiation. CSs quantify the extent that care was guideline-adherent. Linear and logistic regressions controlling for cohort examined Hb outcomes as a function of CSs.

Results: A one-point increase in CS was associated with 0.60 g/dL increase in Hb at month 4 ($R^2 = 0.40$) and 0.56 g/dL increase in Hb change from month 1–4 ($R^2 = 0.33$). Each one-point increase in CS increased the odds of reaching Hb $\geqslant$ 11 g/dL by 3.14 ($R^2 = 0.42$) and Hb $\geqslant$ 12 g/dL by 2.77 ($R^2 = 0.45$).

Conclusion: Guideline-adherent EP treatment may improve Hb outcomes but specifically designed outcomes studies are necessary.

* *Corresponding author:* Address: Matrix45, 620 Frays Ridge Road, Earlysville, VA 22936, USA. Tel.: +1 303 997 2697; fax: +1 978 945 8374.
E-mail address: iabraham@matrix45.com (I. Abraham).

0959-8049/$ - see front matter
doi:10.1016/j.ejca.2008.09.036

1. Introduction

The EORTC guidelines for erythropoietic proteins (EPs)[1,2] provide evidence-based guidance for differential diagnosis, treatment and target outcomes. The RESPOND system is a web-based clinical guidance tool based on these guidelines. It asks clinicians for information on their cancer patients. These data are analysed by means of a set of algorithms based on the EORTC guidelines. Any deviation from the guidelines triggers a diagnostic or treatment recommendation citing the applicable guideline(s). Two validation studies[3] showed that the algorithms were accurate[4]; that anaemia management was more likely to be aligned with the EORTC guidelines when using the RESPOND system; and that system use had an incremental effect above and beyond the pharmacotherapeutic effect of EPs.[5]

As part of the validation methodology, we designed a scoring method to quantify the extent to which the care of an anaemic cancer patient is congruent with the EORTC guidelines. Though the validation study was not designed specifically to examine the association between congruence scores and haemoglobin (Hb) outcomes,[3] we noticed a relationship between both variables. We examined whether practicing in accordance with the EORTC guidelines is associated with better Hb outcomes.

2. Patients and methods

The methodology for the scientific validation of RESPOND has been described in detail elsewhere.[3]

2.1. Sample

The sample consisted of 34 patient pairs (total $N = 68$) matched on the type of cancer and chemotherapy. All patients were adults, diagnosed with a solid or haematological malignancy, treated with chemotherapy, and anaemic (Hb < 11 g/dL). The referent sample consisted of 34 prospectively followed patients whose clinician used the RESPOND system (prospective cohort or 'post-cohort'). The matching sample was composed of patients seen by the same clinicians prior to the introduction of the RESPOND system and managed per their best clinical judgement (retrospective cohort or 'pre-cohort'). See Van Erps and colleagues for a description of the sample.[5] Data were recorded at four time points about one month apart, with the first time point coinciding with the initiation of EP treatment.

The study was conducted at a 360-bed general hospital located in a medium-sized Belgian city (Aalst) chosen because it more closely resembles daily clinical practice than might be found in large academic or small hospitals.

2.2. Congruence score

The congruence score (CS) quantifies the extent to which a patient's anaemia management is in accordance with the EORTC guidelines (Table 1). It is an indication of the diagnostic and treatment patterns over time for a given patient relative to the EORTC guidelines.

2.3. Analysis

Because of the potential influence of cohort membership and thus exposure to RESPOND, we controlled for this variable in linear and logistic regression analyses so that any residual effects observed can be attributed to variability in congruence scores.

3. Results

Differences between the two cohorts in mean Hb were not statistically significant at visit 1 but were significant at visit 4 ($p = 0.007$; Table 2). The differences in proportions of patients in each cohort reaching Hb $\geqslant$ 11 g/dL and Hb $\geqslant$ 12 g/dL at visit 4 were statistically significant (respectively, $p = 0.027$ and $p = 0.038$), and so was the mean change in Hb over time (HbΔ, $p = 0.006$).

Mean congruence scores were 3.00 ± 1.48 for the retrospective cohort and 8.18 ± 1.38 for the prospective cohort ($p < 0.001$).

Table 1 – Calculation of the congruence score (CS).

Item	Scoring
Rule out/treat other causes of anaemia: iron deficiency	+0.25
Rule out/treat other causes of anaemia: bleeding	+0.25
Rule out/treat other causes of anaemia: nutritional deficits	+0.25
Rule out/treat other causes of anaemia: haemolysis	+0.25
ESA treatment initiated at haemoglobin (Hb) range 9.0–11.0 g/dL	+1.00
If Hb < 9.0 g/dL patient was considered for blood transfusion; OR: no need for blood transfusion	+1.00
Anaemic asymptomatic patient with Hb < 11.9 g/dL was considered for ESA treatment on individual basis; OR: patient does not fall in this category	+1.00
Hb target set at Hb range 12.0–13.0 g/dL	+1.00
Initial ESA dose = 40,000IU epoetin alfa Q1W; 30,000IU epoetin beta Q1W; or darbepoetin alfa Q1W or Q3W	+1.00
Initial ESA dose was fixed and not weight adjusted	+1.00
Hb target achieved at 4–8 weeks; if not, individualised dose escalation	+1.00
Hb levels maintained in Hb range 12.0–13.0 g/dL for up to 8 weeks (+125 per week)	+1.00
ESA discontinued if Hb $\geqslant$ 13.0 g/dL	+1.00
Maximum possible score	10.00

Table 2 – Haemoglobin levels.

	All patients	Pre-cohort	Post-cohort	*p*
	M ± SD (95% confidence interval (CI))	M ± SD (95% CI)	M ± SD (95% CI)	
Hb at visit 1 (g/dL)	10.27 ± 0.62 (10.12–10.42)	10.30 ± 0.47 (10.14–10.47)	10.23 ± 0.74 (9.98–10.49)	n.s.
Hb at visit 2 (g/dL)	10.92 ± 1.30 (10.60–11.24)	10.57 ± 1.08 (10.16–10.95)	11.28 ± 1.42 (10.76–11.79)	0.026
Hb at visit 3 (g/dL)	11.35 ± 1.39 (11.02–11.69)	10.97 ± 1.18 (10.55–11.38)	11.76 ± 1.49 (11.23–12.28)	0.019
Hb at visit 4 (g/dL)	11.58 ± 1.54 (11.20–11.96)	11.10 ± 1.40 (10.61–11.59)	12.11 ± 1.53 (11.55–12.67)	0.007
Change in Hb from visit 1 to visit 4 (HbΔ) (g/dL)	1.33 ± 1.64 (0.92–1.73)	0.80 ± 1.51 (0.27–1.33)	1.90 ± 1.61 (1.31–2.49)	0.006
Hb at visit 4	*%*	*%*	*%*	
>11 g/dL	70.8	58.8	83.9	0.027
<11 g/dL	29.2	41.2	16.1	
>12 g/dL	41.5	29.4	54.8	0.038
<12 g/dL	58.5	70.6	45.2	

Linear regression models controlling for cohort were fitted for HbV4 and HbΔ (for both, $p_{fit} < 0.001$; Table 3). Congruence scores accounted for 40% of the variation observed in HbV4, which increased by 0.60 g/dL for each one-point increase in congruence score. Congruence scores also explained 33% of the variation in HbΔ, and each one-point increase was associated with a 0.56 g/dL rise in HbΔ.

Logistic regression models controlling for cohort examined the improved odds of reaching Hb $\geqslant$ 11 g/dL and Hb $\geqslant$ 12 g/dL (for both, $p_{fit} < 0.001$). Congruence scores accounted for 42% and 45% of the respective variances. A one-point increase in congruence score was associated with increased odds of 3.14 for attaining Hb $\geqslant$ 11 g/dL and 2.77 for achieving Hb $\geqslant$ 12 g/dL.

4. Discussion

The principal finding is that congruence scores are independent predictors of Hb levels after 4 months of treatment with EPs, whether expressed in Hb values at visit 4, Hb change scores, or proportions of patients reaching Hb levels $\geqslant$11 g/dL and $\geqslant$12 g/dL. The recent call to use EPs to manage anaemia in cancer patients according to guidelines is underscored by the results reported here.[6] For instance, if a given patient A was managed at a congruence level of 8 compared to a patient B managed at a level of 5, patient A's Hb at visit 4 could be 1.80 g/dL higher and his/her Hb change from visit 1 to 4 could exceed B's by 1.68 g/dL. A's odds of attaining Hb $\geqslant$ 11 g/dL would be 9.42 higher than B's and A's odds of reaching Hb $\geqslant$ 12 g/dL would be 8.41 higher.

With due caution because the data reported here are from a validation and not an outcomes study, with a limited sample size and conducted at one centre, our results nonetheless provide the first evidence that practicing in accordance with the EORTC guidelines translates in improvements in Hb outcomes. This finding must be replicated in multi-centre outcomes studies with larger samples and designed specifically to model the relationships between guideline-congruent anaemia management and Hb outcomes under consideration of potential confounding variables such as type of cancer, disease stage, type and line of chemotherapy treatment and selected demographics. In the interim, there is preliminary evidence that guideline-adherent management of cancer-related anaemia may have significant beneficial effects on Hb outcomes.

Conflict of interest statement

M. Aapro has consulted with, received research grants and contracts from, and/or served as a sponsored speaker for the following companies: Roche, Amgen and Novartis. He declares no conflict with regard to the work described in this manuscript.

J. Van Erps has consulted with, received research grants and contracts from, and/or served as a sponsored speaker for the following companies: Roche and Novartis. She declares no conflict with regard to the work described in this manuscript.

I. Abraham and K. MacDonald have consulted with, received research grants and contracts from, and/or served as a

Table 3 – Summary of regression models.

Linear regression	*F*	$R^2_{Adjusted}$	b_0	b_1	95% CI of b_1
Hb at visit 4	22.05*	0.40	9.30*	0.60*	0.39–0.81
HbΔ	16.39*	0.33	–0.88**	0.56*	0.32–0.80
Logistic regression	–2LL	$R^2_{Nagelkerke}$	Odds ratio		95% of OR
Hb at visit 4 $\geqslant$ 11 g/dL	55.62*	0.42	3.14		1.56–6.30
Hb at visit 4 $\geqslant$ 12 g/dL	61.83*	0.45	2.77		1.67–4.59

Hb = haemoglobin; HbΔ = change in Hb from visit 1 to 4; –2LL = –2 log likelihood; and OR = odds ratio.

* $p < 0.001$.

** $p = 0.044$.

sponsored speaker for the following companies and, as applicable, their subsidiaries: Novartis, Johnson & Johnson (including Centocor, Ortho-Biotech, Janssen Pharmaceutica, Janssen-Cilag and Janssen-Ortho), Eli Lilly, Roche, Pfizer, Amgen, Merck, Bristol-Myers Squibb, Schering-Plough, AstraZeneca, Bayer, GlaxoSmithKline, Lundbeck and Innogenetics (including Xcellentis). Matrix45 has been contracted by sponsor to provide support with project conceptualisation, project design, protocol development, development of project materials, training, project management and implementation, development of statistical plan, and quality assurance. Per company policy, I. Abraham, K. MacDonald and T. Albrecht are barred from holding equity in any client companies and are subjected to internal and external review of their work to assure objectivity and transparency. They have taken the necessary steps to assure independence and do not declare a conflict of interest with regard to the work described in this manuscript.

P. Soubeyran has consulted with, received research grants and contracts from, and/or served as a sponsored speaker for the following companies: Roche, Amgen, Johnson & Johnson, Sanofi-Aventis, Schering AG, Schering-Plough, Pfizer, Chugai and Baxter Oncology. He declares no conflict with regard to the work described in this manuscript.

M. Turner and H. Warrinnier are employees of F. Hoffmann-La Roche and its subsidiaries. They have refrained from undue influence throughout the project and manuscript preparation.

T. Albrecht has consulted with the following companies: Roche, Novartis and Schering-Plough. She does not declare a conflict of interest with regard to the work described in this manuscript.

Disclosure of associated publications

Abstracts

1. Foubert J, Aapro M, Soubeyran P, Bokemeyer C, Van Erps J, Muenzberg M, Turner M, MacDonald K, Abraham I. Intraclass correlation metrics for the accuracy of algorithmic definitions in a computerized evidence-based support system for the use of erythropoietic proteins in cancer-related anemia. J Clin Oncol 2007;25(suppl 18):S19633.
2. Van Erps J, Aapro M, MacDonald K, Soubeyran, P., Muenzberg M, Dunlop R, Warrinnier H, Abraham I. Promoting evidence-based management of anemia in cancer patients: Background and scientific validation of RESPOND, a web-based clinical decision-support system. J Clin Oncol 2007;25(Suppl 18):S19676.
3. Van Erps J, Aapro M, MacDonald K, Soubeyran P, Muenzberg M, Albrecht T, Warrinnier H, Abraham I. Evidence-based management of anemia in cancer patients: validity of RESPOND, a web-based clinical guidance system based on the EORTC guidelines. J Clin Oncol 2008;26(Suppl):S20573.
4. Van Erps J, Aapro M, MacDonald K, Soubeyran P, Muenzberg M, Albrecht T, Warrinnier H, Abraham I. Validation of RESPOND, a web-based clinical guidance system based on the EORTC guidelines for the use of erythropoietic proteins in cancer patients with anemia. Haematol/Hematol J 2008;93(Suppl):999.

Articles

1. Aapro M, Abraham I, MacDonald K, Foubert J, Soubeyran P, Bokemeyer C, Van Erps J, Muenzberg M, Turner M. Intraclass correlation metrics for the accuracy of algorithmic definitions in a computerized decision-support system for supportive cancer care. Support Care Cancer 2007;15:1325–29.
2. Aapro M, MacDonald K, Van Erps J, Soubeyran P, Turner M, Muenzberg M, Dunlop R, Abraham I. Promoting evidence-based management of anemia in cancer patients: background, development and scientific validation of RESPOND, a web-based clinical guidance system based on the EORTC guidelines. Crit Rev Oncol Hematol 2008;65:32–42.

Acknowledgements

Supported by grants from F. Hoffmann-La Roche AG. The authors thank Matthew Abraham for editorial support.

REFERENCES

1. Bokemeyer C, Aapro MS, Courdi A, et al. EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer. *Eur J Cancer* 2004;**40**:2201–16.
2. Bokemeyer C, Aapro MS, Courdi A, et al. EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer: 2006 update. *Eur J Cancer* 2007;**43**:258–70.
3. Aapro M, Van Erps J, MacDonald K, et al. Promoting evidence-based management of anemia in cancer patients: background, development, and scientific validation of RESPOND, a web-based clinical guidance system based on the EORTC guidelines. *Crit Rev Oncol Hematol* 2008;**65**:32–42.
4. Aapro M, Abraham I, MacDonald K, et al. Intraclass correlation metrics for the accuracy of algorithmic definitions in a computerized decision support system for supportive cancer care. *Support Care Cancer* 2007;**15**:1325–9.
5. Van Erps J, Aapro M, MacDonald K, et al. Promoting evidence-based management of anemia in cancer patients: concurrent, and discriminant validity of RESPOND, a web-based clinical guidance system based on the EORTC guidelines [submitted for publication].
6. Aapro M, Birgegard G, Bokemeyer C, et al. Erythropoietins should be used according to guidelines. *Lancet Oncol* 2008;**9**:412–3.