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REVIEW
2007 Standards, Options, and Recommendations: Use of Erythropoiesis-Stimulating Agents (ESA: Epoetin Alfa, Epoetin Beta, and Darbepoetin) for the Management of Anemia in Children With Cancer

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The Standards, Options, and Recommendations (SOR) project undertaken by the French National Federation of Cancer Centers (FNCLCC) to develop and disseminate clinical practice guidelines in oncology has now been taken over by the French National Cancer Institute. In 2007, the SOR updated the information related to the use of erythropoiesis-stimulating agents (ESA) in anemic children with cancer. Updates were based on a review of the most reliable scientific data available, followed by critical appraisal by a multidisciplinary group of experts and validation by independent experts. The literature review identified four randomized trials likely to provide reliable new information on the use of ESA in children. This review confirmed four points: treatment increases hemoglobin levels and decreases the need for blood transfusions; no quality-of-life and no survival benefit has been demonstrated; treatment does not seem associated with significantly more side effects; impact on thromboembolic events and patient quality of life remains unclear. The main result of the study was the elaboration of a new standard of care unavailable at the time of the 2003 version. Systematic administration of ESA is not recommended for the prevention or treatment of anemia in pediatric cancer patients. However, treatment decision must be made on a case-by-case basis and, when treatment is considered, the intravenous route must be preferred. The full French document is available at www.sor-cancer.fr. Pediatr Blood Cancer 2009;53:7–12. © 2009 Wiley-Liss, Inc.

Key words: anemia; cancer; children; clinical practice guidelines; epoetin; ESA

INTRODUCTION

Standards, Options, and Recommendations Project

The Standards, Options, and Recommendations (SOR) project, undertaken by the French National Federation of Cancer Centers (FNCLCC) in 1993, has now been taken over by the French National Cancer Institute. The project involves the development and updating of evidence-based clinical practice guidelines (CPG) in oncology, their dissemination to practitioners, and assessment of their impact on clinical practice.

Methodology

A literature review followed by critical appraisal of new data by a multidisciplinary working group of experts. The CPG were defined following the procedure developed by the SOR program, then reviewed by independent experts. Details of this methodology have been published [1] and are also available on the SOR website (www.sor-cancer.fr).

In summary, a literature search was performed for dates between November 2003 and February 2007, to identify all available information on the use of erythropoiesis-stimulating agents (ESA). Following the selection and critical appraisal of published results, the working group developed draft guidelines, presented levels of evidence along with experts opinion. The document was peer-reviewed by independent experts, according to an international appraisal instrument for assessing the quality of clinical practice guidelines (AGREE grid) [2]. Experts' comments were incorporated in the final version of the CPG validated in December 2007.

Recommendations are based on evidence synthesis and transparent expert opinion. The CPG are an information tool designed to assist clinicians in making decisions about patient management in specific clinical situations. Their aim is to improve the quality and efficiency of care provided to cancer patients. Recommendations are classified as Standards or Options as follows: a standard is any clinical strategy unanimously recognized as the ''gold standard'' of care by clinical practitioners, whereas options represent the different clinical strategies which may be found appropriate in a given clinical context. One of the options can be preferred. When justified, the decision can be to include the patient in a randomized clinical trial.

Implementation of the recommendations must take into account both the regional healthcare context and patient preferences. The type of evidence underlying each recommendation is indicated using a classification developed by the SOR based on previously published methods. The level of evidence depends not only on the type and quality of the studies reviewed, but also on the agreement between results (Table I). When there was no clear scientific evidence, judgment was made according to the professional experience and consensus opinion of the experts group (experts' agreement), then validated by peer-review.

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TABLE I. Definition of Levels of Evidence

Level	Definition
A	There exists a high-standard meta-analysis or several high-quality randomized clinical trials which provide consistent results
B	There exists good quality evidence issued from randomized trials (B1) or prospective or retrospective studies (B2). The results are consistent when considered together
C	The methodology of the available studies is weak or their results are not consistent when considered together
D	Either scientific data do not exist or there is only a series of cases

Intellectual Property

BACKGROUND AND OBJECTIVES OF THE CURRENT STUDY

In 1998, a multidisciplinary expert group commissioned by the FNCLCC published the first recommendations for the use of erythropoietin in cancer patients in France [3]. Updates were issued periodically thereafter (in 1999 [4], in 2003 [5]). The first version, as well as the 2003 update, were based on the results of several phase II [6,7] and randomized phase III [8,9] pediatric studies. With schedules similar to those currently used in adults, these studies reported good clinical efficacy and tolerance of erythropoietin in children. However, interpretation of these results was limited because the studies were performed on small cohorts of patients and used inconsistent designs and methods: patients with different histological diagnoses, heterogeneous inclusion criteria (especially baseline hemoglobin levels), various patterns of ESA administration (doses between 25 and 400 IU/kg, 1 daily to 3 weekly injections, intravenous or subcutaneous route, treatment duration between 14 days and 11 months), and different hemoglobin starting levels (Hb <6 g/dl, or <7 g/dl, or <10 g/dl). The 2003 recommendations are described in Table II.

A scientific monitoring program initiated in 2006 identified new factors that should be taken into account in elaborating the recommendations. The monitoring report published in 2007 is available on the SOR website at www.sor-cancer.fr.

The present article presents the 2007 update of clinical guidelines for the use of ESA in anemic children with cancer. The full French version of the 2007 document, including information on the other clinical variables studied, a detailed synthesis of the existing literature and the conclusions published, as well as the critical appraisal of experts in the field, is available on the SOR website at www.sor-cancer.fr.

RESULTS

Bibliography Results

The literature search for articles published between November 2003 and February 2007 identified four randomized studies of interest [10–13].

Analysis of Data

Of the four randomized studies selected, two had been performed in children with solid tumors [10,12] and two included children with either solid or lymphoid tumors [11,13]. In all four trials, the treatment schedule was similar to those used for adult patients. The usual dosage is 600 units/kg/week, with a maximum of 40,000 units. In children achieving a <1 g/dl Hb increase from baseline, the dose can be increased to 900 units/kg/week, with a maximum of 60,000 units (Table III).

The first study (34 patients) [10] demonstrated that tolerance to EPO alfa treatment is generally good, with significantly increased hemoglobin levels (10.21 g/dl vs. 8.41 g/dl, $P = 0.027$) and a significant decrease of the number of transfused patients (5.9% vs. 47.0%, $P = 0.008$).

In the second study (224 patients) [11], the authors report a significantly increased proportion of Hb responders (56.5% vs. 34.9%, $P = 0.002$) and a non-significant decrease of the number of transfused patients (64.9% vs. 77.5%, $P =$ ND). No quality of life benefit from ESA could be detected, with no statistically significant change from baseline in either patient-reported PedsQL-GCS total score or patient- and parent-reported individual domains of the PedsQL Cancer Module. More clinically relevant thrombotic vascular events were reported in the group of patients receiving ESA, but this increase was not statistically significant (5.4% vs. 1.8%, $P =$ not reported).

Results of the third study (217 patients) [13], which used the same data set as the study conducted by Razzouk et al. [11], showed no difference in quality of life (PedsQL-I) between ESA- and

TABLE II. 2003 Standards and Options: Recommendations

Standard
No standard
Options
Human erythropoietin (rHuEPO) treatment can be administered to children with cancer on a case-by-case basis when there is a contraindication, either relative or absolute, to the use of transfusions (cultural or religious pressure, rare blood group, immunized patient, etc.) (experts' agreement)
When rHuEPO treatment is considered, administration by the intravenous route is recommended (experts' agreement)
Large scale, prospective randomized trials are required to assess the benefit of rHuEPO in children with cancer (experts' agreement)

TABLE III. Indication of ESA in Children With Cancer: Results of Randomized Phase III Trials

References Period of inclusion	Nb of patients I/A Follow up	Patient characteristics	Treatment	Outcomes	Arm A	Arm B	p	Toxicity
[10] NR	34 included 8 weeks	Solid tumor= 100% Hb < 10 g/dL CT +/- RT 14 girls - 20 boys median age: 5 years	Arm A (n=17): EPO alfa 150 IU/kg, 3x/week over 2 months Arm B (n=17): control	Hb level	10.21 g/dL	8.40 g/dL	p=0.027	Good tolerance
				Percentage of patients transfused	5.9 %	47.0 %	p=0.008	
[13] NR	217 / 217 (Hb level) 217 / 207 (QoL) NR	hematologic or solid tumors 5-18 years CT baseline Hb level unknown	Arm A (n=108): i.v. EPO alfa 600 IU/kg Arm B (n=109): placebo	QoL / PedsQL-I: age group versions: (5-7 yrs; 8-12 yrs; 13-18 yrs)	In both groups, responders (to Hb treatment) have better QoL than non responders		p NR	NR
				Rate of responders (Hb increase ≥ 2 g/dL)	56.5 %	34.9 %	p=0.0017	
[11] September 2000 to September 2003	224 / 222 16 weeks	Solid tumors = 36% HD = 14% ALL = 36% NHL = 12% 5-18 years -Hb < 10.5 g/dL for boys and girls, 5-12 yrs -Hb < 11.0 g/dL for girls >12 yrs -Hb < 12.0 g/dL for boys >12 yrs	Arm A (n=113): i.v. ESA 600-900 IU/kg 1x/week Arm B (n=111): placebo	QoL / PedsQL-GCS	74.9 ± 15.22	75.5±15.74	p=0.763	Serious adverse events: 68.8% (A) vs. 74.5% (B) Clinically relevant thrombotic events: 5.4% (A) vs. 1.8% (B); p NR Thrombotic vascular events (clotted line, or chest pain, or edema): 22.3% (A) vs. 22.7% (B) p NR
				Quality of life / PedsQL 3.0-cancer	No significant difference between the 2 arms in the different domains		0.238<p<0.728	
				Percentage of Hb response (2.0 g/dL increase since day 0)	56.5 %	34.9 %	p=0.002	
				Percentage of patients transfused	64.9 %	77.5 %	p NR	
[12] January 1992 to January 1997	38 included NR	metastatic neuroblastomas > 1 year Hb > 8.0 g/dL and < 13 g/dL	On day 6 of CT: Arm A (n = 18) : G-CSF + ESA Arm B (n = 20) : G-CSF	Median total number of transfusions per patient	13.5	9.5	p NR	No difference between the two groups for duration and incidence of febrile neutropenia
				Overall survival at 5 years	44.4 % ± 11.7 %	40.0 % ± 10.3 %	p=0.71	
				Progression-free survival at 5 years	38.9 % ± 11.5 %	25.0 % ± 8.8 %	p=0.72	
				Hb decrease	0.1 g/dL	0.8 g/dL	p=0.35	
				Response to CT	71 %	67 %	p=1.0 95 % CI, 65.7 %92.3 %	

Nb, number; Hb, hemoglobin; ESA, erythropoiesis-stimulating agents; CI, confidence interval; CT, chemotherapy; GCS, Generic Core Scale; G-CSF, granulocyte colony-stimulating factor; I/A, included/assessed; NR, not reported; PedsQL-I, Pediatric Quality of Life Inventory; QoL, quality of life; RT, radiotherapy; HD, Hodgkin disease; ALL, acute lymphocytic leukemia; NHL, non-Hodgkin lymphoma.

placebo-treated patients. However, the authors demonstrated a significant correlation between higher hemoglobin levels ($\geq$2 g/dl increase) and improved quality of life in both groups. Their conclusion was that both ESA treatment and transfusion can be used to address the quality of life issues associated with low hemoglobin levels.

Finally, the fourth study (38 patients) [12] assessed the efficacy of ESA and granulocyte colony-stimulating factor (G-CSF) administration in reducing blood transfusion requirements, stimulating hematopoiesis and response to chemotherapy, and prolonging survival in children with high-risk neuroblastoma. The conclusion was that the addition of ESA to G-CSF provides no benefit for these patients. However, because the randomization procedure used in this study was very different from other studies (introduction of G-CSF) and the number of randomized patients was very low (n = 38), these results should be viewed with caution.

As a whole, the four studies had relatively homogeneous results regarding treatment efficacy. Concerning toxicity, only two studies provide information about the incidence of side effects, and the impact of ESA on thromboembolic events remains unclear. Only one of four studies has analyzed this incidence carefully, but details of the exploration are not given and the study population is too small to draw meaningful conclusions.

Expression of ESA Receptors (ESA-R) by Tumor Cells

If a number of reports on ESA in cancer patients have raised safety concerns, some studies, both published and unpublished, have shown a detrimental effect on survival or tumor response in the adult population. Considering these data, the US Food and Drug Administration provided an additional series of recommendations in May 2007. These recommendations included setting a baseline Hb level at which to initiate ESA therapy in asymptomatic patients, reassessing anemia at the start of each new chemotherapy regimen, restricting the use of ESA to certain tumor types, further restricting ESA indications on the US Food and Drug Administration-approved label, and encouraging the conduct of future clinical trials [14].

Analysis of the literature provided information on the expression of ESA receptors in some tumor cells and the putative role of erythropoietin-stimulating agents in tumor proliferation and survival reduction [15–25]. This possible involvement of ESA in tumor proliferation is a major ethical concern, especially in the context of childhood malignancies in which prognosis is usually good with overall survival close to 75%. Thus, the risk-benefit ratio of ESA on overall childhood cancer survival appears unacceptable. The central issue is whether functional ESA receptors capable of specifically binding ESA and activating intracellular signaling pathways are expressed on the tumor cell membrane. A survey of the literature on the subject, principally in adult malignancies, produced conflicting results [15,16] and the exact role of these receptors on the biology of the tumors remain unclear.

Interestingly, the specificity of the antibody (Santa-Cruz C-20; cat # sc-695) used for immunohistological detection of ESA-R was recently called into question. This antibody not only fails to discriminate between membrane and intracellular receptor expression, as shown in the manuscript by Longmore [17], but also is not specific for ESA-R, since it detects other proteins, notably heat shock protein 70 (HSP70) [18]. The expression of ESA-R may thus simply indicate the presence of HSP70 in the tumor cells tested. Therefore, preclinical data available on the role of ESA and ESA-R expression in tumor cells should be interpreted with extreme care. Several groups have explored the regulatory effect of ESA on tumor growth using xenografts of various human malignant cell lines [21,22]. Their findings suggest that ESA contributes to the growth, viability and angiogenesis of most malignant tumors, and that ESA involvement in tumor proliferation is activated by hypoxic stimulation. However, evidence supporting the binding of ESA to tumor cells and the activation of intracellular signaling pathways is inconclusive.

To date, no animal tumor study has demonstrated a role for ESA alone in promoting tumor growth or decreasing survival. Nonetheless, ESA-R and ESA expression has been reported in common pediatric tumor cells from patients with neuroblastoma, Ewing sarcoma, brain tumor (medulloblastoma, astrocytoma, and ependymoma), Wilms tumor, rhabdomyosarcoma or hepatoblastoma, and in cell lines derived from some of these tumors [24,25]. Batra et al. [25] suggest that the expression of erythropoietin in these tumor cell lines is hypoxia-inducible, and that exogenous erythropoietin increases the production and secretion of angiogenic growth factors, vascular endothelial growth factor, or placenta growth factor from the tumor cell lines, thus promoting endothelial cell proliferation and chemotaxis. These data confirm that a careful evaluation of the impact of ESA is warranted in vivo, first in xenograft models of pediatric tumors, then in pediatric patients with cancer.

In the American Society of Hematology Clinical Practice Guideline Update, Rizzo et al. [14] concluded that priorities for future research include increased effort, using both basic laboratory and clinical research, to understand the functional impact and clinical consequences of exposing tumors with erythropoietin receptors to exogenous ESA. Considering that insufficient information is available in children with malignancies and that the prognosis of pediatric tumors is generally excellent, the group of experts decided to adopt the precautionary principle and recommended that ESA treatments be discontinued until reasonable safety is assured.

TABLE IV. Indication of ESA in Children With Cancer: Summary of Conclusions

	Hb level	Transfusion needs	Quality of life	Toxic effects	Survival
Conclusions	Benefit	Benefit	No sign of improvement	No sign of increased toxicity	Impact not demonstrated
Study type: number	RCT: 4	RCT: 3	RCT: 1	RCT: 2	RCT: 1 (P = NS)
Consistency between studies	Yes	Yes	NA	Yes	NA
Level of evidence	B1	B1	C	C	NE

NA, not applicable; NE, not evaluated; NS, not significant; RCT, randomized controlled trial.

CONCLUSIONS

Conclusions and Detailed Expert Advice

Evidence indicates that in children with cancer (either solid or hematological malignancies), ESA promotes increased levels of hemoglobin, thus reducing the need for blood transfusions; ESA does not appear, however, to improve quality of life in children with solid or hematological cancers. There is no conclusive evidence of an effect of ESA on survival, and ESA administration does not appear to be associated with a significant risk of toxicity in children with cancer (Table IV).

Although published data provide evidence of hematological improvement with ESA, the effect of ESA treatment on tumor growth, thromboembolic events and quality of life remains uncertain. ESA administration to anemic children with cancer is thus not recommended on a routine basis. Prospective randomized studies are needed to confirm the contribution of ESA to the treatment of these patients, notably with regard to quality of life and toxicity. From available evidence, we also conclude that, when ESA supplementation is being considered, it should be administered by intravenous route which is feasible, safe, and less painful than the subcutaneous route.

Recommendations 2007

Based on data from the literature, conclusions of the working group and expert's comments, we propose an alternative standard that was not available in the SOR 2003 version. The SOR 2007 recommendations on the use of ESA for the management of anemia in children with cancer are as follows:

(1) Systematic administration of ESA is not recommended for the prevention or treatment of anemia in pediatric cancer patients.
(2) The decision of whether to administer ESA to children with cancer must be considered on a case-by-case basis, when there is a contraindication, either relative or absolute, for transfusion (cultural or religious pressure, rare blood group, immunized patient). When ESA administration is considered, the intravenous route should be preferred.

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