Living with Cancer-related Anaemia – What Is the Reality?

a report by
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Anaemia is defined as an imbalance between the production and destruction, or loss, of red blood cells (RBCs), leading to decreased RBC count, haemoglobin (Hb) content and oxygen-carrying capacity of the blood. It can be defined further by graded classification systems, Hb trigger values, tumour type and symptoms. Various classification systems are used to grade the severity of anaemia, from mild to life-threatening, on the basis of Hb concentrations (see *Table 1*). However, anaemia is more than an Hb level. It is a complex condition that impacts many body systems to produce a diverse range of symptoms that include effects on the central nervous, gastrointestinal, vascular and cardiorespiratory systems, as well as the genital tract (see *Figure 1*).[1]

Underdiagnosis of Anaemia in Cancer

Approximately 20–60% of cancer patients have anaemia at presentation[2] and several factors may induce or exacerbate the condition, influencing incidence rates in specific patient groups. These factors include tumour type,[3,4] disease stage,[4,5] duration, intensity and type of treatment[1,2,3,6–8] and patient age.[9]

Despite the high incidence of cancer-related anaemia, it is frequently underdiagnosed and undertreated.[10] A survey of 284 oncologists treating 4,888 cancer patients throughout France, Germany, Italy, Spain and the UK revealed that 52% of patients (out of 3,067 patients with Hb data available) had Hb concentrations of ≤12g/dl. However, only 22% of this group were diagnosed as anaemic by their physician.[10] This may reflect an underappreciation of the seriousness of anaemia and its impact on the patient, as well as practical difficulties in diagnosing often vague, emotional and psychological symptoms.

Causes of Anaemia in Patients with Cancer

The causes of anaemia in patients with cancer fall into three distinct categories: anaemia that occurs as a result of the malignancy, anaemia attributed to the cancer therapy and anaemia caused as a result of other contributing factors, such as infections, nutritional deficiencies and underlying chronic disorders in addition to the cancer.[27]

Anaemia of Chronic Disease

Anaemia of chronic disease, in the absence of any treatment-related factors, is not fully understood, but it is represented by usually mild (>9g/dl) normochromic or hypochromic anaemia with a disproportionately low reticulocyte count relative to the severity of anaemia.[11] Furthermore, RBC survival is shortened, possibly due to the action of immune and inflammatory cytokines activated by the presence of the tumour and an imbalance develops between RBC production and depletion, as a result of the inability of the bone marrow to produce RBCs at a rate sufficient to compensate for their reduced lifespan. This is thought to reflect the suppression of erythroid progenitor cells, impaired iron utilisation and inadequate production of endogenous erythropoietin (EPO) by the underlying malignancy.[11,12] Other disease-related factors include direct bone-marrow involvement of the malignancy, haemolysis, blood loss associated with the tumour, renal insufficiency and hypersplenism.

Treatment-related Anaemia

The extent to which treatment for cancer can induce or exacerbate anaemia varies considerably according to the type of tumour and the treatment administered.[2,4] Myelosuppressive, cytotoxic chemotherapy or radiotherapy, which involves large areas of bone marrow, will compromise bone marrow function such that the production and maturation of RBCs are reduced and anaemia follows.[2,3,6–8] As the kidney is a primary site of endogenous EPO production, nephrotoxic drugs, including cisplatinum-based chemotherapy, may decrease the production of EPO via drug-induced renal tubular damage.[12] Other possible treatment-related causes of anaemia include long-term damage to the stem cell pool or nutritional deficiencies as a result of radiotherapy and blood loss during extensive surgery.[9]

Cancer Anaemia and Fatigue

Fatigue is the most commonly reported clinical manifestation of anaemia in cancer patients,[13,14] with 78% of patients experiencing symptoms.[14] Fatigue is not relieved by sleep or rest and is not exacerbated by exertion. However, Hb concentration has been shown to have a considerable impact on the incidence of fatigue and subsequently on quality of life (QoL). In a study of 50 patients with solid tumours or haematological malignancies, those with Hb levels ≤12g/dl reported significantly more fatigue, worse physical and functional wellbeing and generally reduced QoL than those who had Hb ≤12g/dl.[15] The relationship between Hb concentration and QoL changes was further defined in a retrospective analysis of data from two community studies that enrolled 4,382 anaemic cancer patients receiving chemotherapy.[16] In these patients, the maximum QoL gain occurred in those whose Hb concentration was increased to ≤12g/dl (range 11–13g/dl).[16]

Patients rather than their physicians provide the best documentation of fatigue. Data from a survey of 419 cancer patients reiterated the negative impact and wide range of effects that fatigue has upon daily life (see *Figure 2*). More than 50% of patients reported that their ability to work, physical wellbeing, ability to enjoy life in the moment and emotional wellbeing were all 'somewhat' or 'very much' affected by fatigue.[14] However, fatigue remains poorly understood and patients and oncologists differ in their perception of the importance of treating fatigue.[14] When asked which factors affected their everyday life the most, 60% of patients ranked fatigue highest, followed by nausea (22%), depression (10%) and pain (6%).[17] Interestingly, 41% of patients but

only 5% of oncologists felt that it was more important to reduce/relieve fatigue than pain (see *Figure 3*).[14]

Assessment of Cancer-related Anaemia and Fatigue

The assessment of cancer-related anaemia is based primarily on quantitative measures of haematocrit (Hct) or Hb, with considerably less emphasis placed on patient symptoms, changes in function or QoL. Furthermore, rather than long-term monitoring of patients' symptoms alongside these quantitative indicators in order to establish trends, considerable reliance is placed on single measures. Anaemia is often, therefore, considered in a single dimension and the symptoms that most directly affect patients' lives, such as fatigue, are not fully evaluated. However, cancer-related fatigue has now been accepted as a diagnosis in the 10th revision of the International Classification of Diseases and an algorithm has been proposed for its evaluation and management.[18] Assessment of cancer-related fatigue has also been aided by the creation of a defined list of diagnostic criteria (see *Table 2*).[13]

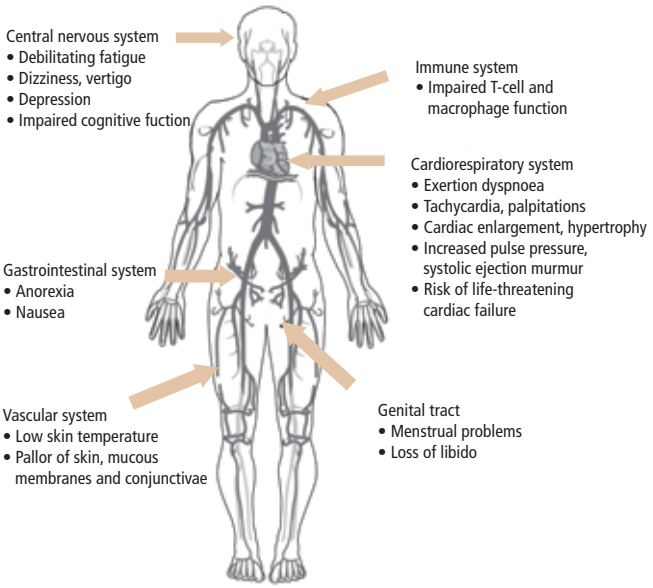
A variety of tools is available to assess cancer-related fatigue. In the clinical setting, where there is limited time for detailed evaluation, assessment may be performed by asking simple questions such as "Are you experiencing any fatigue?" and "How severe has your fatigue been during the past week on a scale of one to 10?" However, multidimensional questionnaires provide further information on the patient's symptoms and are more commonly used in the research setting.[16,18] The Piper Fatigue Scale is an early example of a validated multidimensional instrument that uses a 41-item questionnaire to evaluate severity, distress and the impact of fatigue in patients receiving radiotherapy, although it may also be used in other patient groups.[18] The Functional Assessment of Cancer Therapy-General (FACT-G) scale is a 20-item scale that is commonly used to assess general QoL. FACT-G has been supplemented by the addition of fatigue- and anaemia-specific subscales; the FACT-Fatigue (FACT-F) subscale employs the core FACT-G with 13 additional items; while the FACT-Anaemia (FACT-An) subscale employs seven items in addition to those of the FACT-F.[15,19]

Multidimensional fatigue assessment tools, although valuable in the research setting, are time-consuming and, consequently, may be used inconsistently. This highlights the need for the development of a more suitable assessment method that is compatible with the reality of healthcare assessment in European hospitals. An ideal assessment tool would consist of a minimum number of questions required to reach an accurate diagnosis and evaluation of fatigue. An accurate assessment of the level of fatigue would allow the healthcare professional to provide the patient with an explanation for their symptoms and to relate fatigue to disease, treatment or other concomitant conditions (e.g. anaemia, metabolic disturbances and pain).

Treatment of Cancer Anaemia and Fatigue

Historically, RBC transfusions have been the cornerstone of management for severe cancer-related anaemia, as they rapidly raise the RBC count and Hb concentration. However, the benefits of RBC transfusions are transient and potential risks include infection, haemolytic reactions and transfusion-related lung injury.[2,20] Furthermore, a UK audit of 2,719 cancer patients receiving chemotherapy revealed that there is no general consensus between different clinical centres regarding the 'transfusion trigger' (the mean Hb concentration at which RBC transfusion is implemented), so treatment is not standardised.[6]

Figure 1: Signs and Symptoms of Anaemia



Source: Ludwig et al., 1998.[1] Adapted with permission from Elsevier.

Table 1: Quantitative Definitions of Anaemia Severity[2]

Grade	Severity	Serum Hb levels (g/dl)		
		WHO	SWOG	NCI/ECOG/ CALGB/GOG
1	Mild	9.5–10.9	10–WNL	10–WNL
2	Moderate	8–9.4	8–9.9	8–10
3	Serious/severe	6.5–7.9	6.5–7.9	6.5–7.9
4	Life-threatening	<6.5	<6.5	<6.5

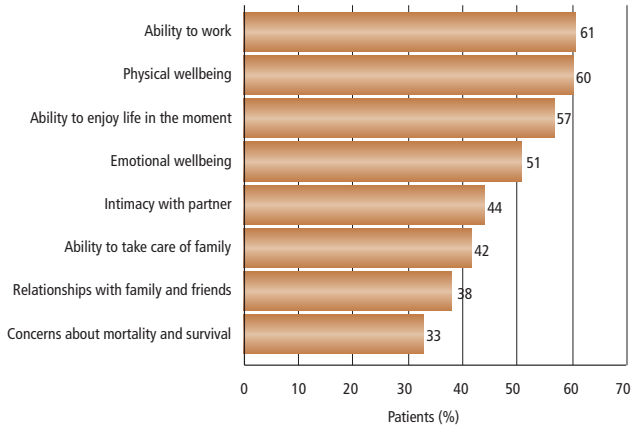
WHO = World Health Organization; SWOG = Southwest Oncology Group; NCI = National Cancer Institute; ECOG = Eastern Co-operative Oncology Group; CALGB = Cancer and Leukemia Group B; GOG = Gynecological Oncology Group; WNL = within normal limits. Source: Groopman et al., 1999.[2] Adapted with permission from Oxford University Press.

A valuable alternative to RBC transfusions is the use of the erythropoietic proteins, recombinant human erythropoietin (rHuEPO; epoetin alpha, epoetin beta) and darbepoetin alpha. These therapies mimic the role of endogenous EPO and thus aid in the management of anaemia. An abundance of data demonstrates that erythropoietic proteins increase Hb levels, improve QoL and reduce RBC transfusion requirements in anaemic cancer patients receiving or not receiving chemotherapy.[21–25]

In a randomised, double-blind study of 375 anaemic cancer patients receiving non-platinum chemotherapy, 359 of whom were analysed for efficacy, treatment with epoetin alpha 150IU/kg three times per week (TIW) for up to 28 weeks produced significantly greater increases in Hb concentration ($p<0.001$) and Hb response rate (an increase in Hb ≤2g/dl in the absence of RBC transfusion; $p<0.001$) than placebo.[22] Significantly greater improvements in all primary cancer- and anaemia-specific QoL domains ($p<0.01$) including fatigue, as measured by the FACT-F subscale ($p<0.004$), were noted with epoetin alpha compared with placebo. There was also a statistically significant correlation between change in Hb level and all primary QoL parameters (range $p=0.0002–0.0325$), including fatigue ($p=0.0002$).[22]

Similarly, in a randomised trial in 343 anaemic patients receiving chemotherapy for haematological malignancies, treatment with epoetin beta 150IU/kg TIW for up to 16 weeks resulted in significantly higher Hb

Figure 2: Percentage of Cancer Patients (n=419) Reporting Aspects of Daily Routine That Were 'Very Much' or 'Somewhat' Affected by Fatigue



Source: Vogelzang et al., 1997.[14] Adapted with permission from Elsevier.

response rates than placebo (67 versus 27%; p<0.001).[23] However, when the impact of epoetin beta on QoL was assessed, no statistically significant differences were found on the FACT-F and FACT-An subscales compared with placebo.[23] When the subpopulations of responders and non-responders to epoetin beta were further analysed, statistically significant differences were seen in favour of the responders group for the overall FACT-An QoL (p<0.05) and FACT-F subscale scores (p<0.01).[28]

Darbepoetin alpha, a newer erythropoietic agent, has an extended half-life[26] compared with epoetin alpha and epoetin beta, as well as increased biological activity, allowing for less frequent dosing. In a double-blind, randomised, placebo-controlled study of 314 anaemic lung cancer patients receiving platinum chemotherapy, patients who received darbepoetin alpha 2.25µg/kg once per week (QW) for up to 12 weeks had a significantly greater haematopoietic response rate (an increase in Hb ≤2g/dl, or an Hb concentration ≤12g/dl in the absence of RBC transfusion: 66 versus 24%; p<0.001) than the placebo group.[25] Darbepoetin alpha also resulted in a greater improvement in FACT-F scores compared with placebo (p=0.019).[25] Similar results were reported for 344 patients receiving darbepoetin alpha for up to 12 weeks during concurrent chemotherapy for lymphoproliferative malignancies. The haematopoietic response rate was 65% with darbepoetin alpha and 24% with placebo (p<0.001).[21] Furthermore, the mean increase in the FACT-F subscale score from baseline was significantly greater for darbepoetin alpha than for placebo (p=0.032). Ongoing studies are investigating the feasibility of administering darbepoetin alpha at less frequent dosing intervals of once every two weeks and once every three weeks.

Anaemia May Be an Adverse Prognostic Factor in Patients with Cancer

Increasing evidence suggests that anaemia adversely affects survival in patients with cancer. In a systematic review of 60 papers reporting the survival of cancer patients in relation to anaemia and Hb concentration, Caro and colleagues reported a 65% increase in the relative risk of death for anaemic patients.[27] Similarly, in patients with chronic lymphocytic leukaemia, anaemia and thrombocytopoenia at diagnosis were strongly indicative of poor outcomes.[28] Anaemia at diagnosis has been reported as an independent adverse prognostic factor in patients with Hodgkin's disease[29] or non-Hodgkin's lymphoma.[30]

Whether increasing Hb concentrations could have a positive effect on outcome is a matter of ongoing debate. A link has been made between increased serum Hb concentration and improved survival and QoL in cancer patients.[16,27,31–32] In the study by Littlewood and colleagues, a trend towards increased survival was observed in patients receiving rHuEPO versus placebo; the 12-month estimates of survival were 60 and 49%, respectively.[22] These data must be interpreted with extreme caution, as this study was not powered to address survival.

Recently, a randomised, placebo-controlled study of 939 patients receiving chemotherapy for metastatic breast cancer was terminated early due to higher mortality in the epoetin alpha arm than in the placebo arm at 12 months.[33] However, the authors remarked that the study suffered from problems in design, conduct and post-trial analysis, and other comments and editorials have since been published on this study. Another study of 351 patients with head and neck cancer receiving radiotherapy and epoetin beta 300IU/kg TIW reported poorer tumour outcomes and survival than those receiving placebo.[34] Again, these data must be regarded very cautiously, as more than 30% of patients did not receive radiotherapy per protocol and a further 8% had major protocol violations. Furthermore, when data were analysed for

Table 2: Proposed Criteria for the Diagnosis of Cancer-related Fatigue[7]

A.	Six or more of the following symptoms have been present every day or nearly every day over a two-week period during the last month, and at least one of these symptoms is significant fatigue.
	• Significant fatigue, diminished energy, increased need to rest, disproportionate to any recent change in activity level
	• Complaints of generalised weakness or limb heaviness
	• Diminished concentration or attention
	• Decreased motivation or interest to engage in usual activities
	• Insomnia or hypersomnia
	• Experience of sleep as unrefreshing or non-restorative
	• Perceived need to struggle to overcome inactivity
	• Marked emotional reactivity (sadness, frustration or irritability) to feeling fatigued
	• Difficulty completing daily tasks attributed to feeling fatigued
	• Perceived problems with short-term memory
	• Post-exertional malaise lasting several hours
B.	The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning
C.	There is evidence from the history, physical examination or laboratory findings that the symptoms are a consequence of cancer or cancer therapy
D.	The symptoms are not primarily a consequence of co-morbid psychiatric disorders such as major depression, somatisation disorder, somatoform disorder or delirium

Source: Cella et al., 1998.[13] The symptoms listed in A also relate to statements B, C and D. Reproduced with permission from the National Comprehensive Cancer Network.

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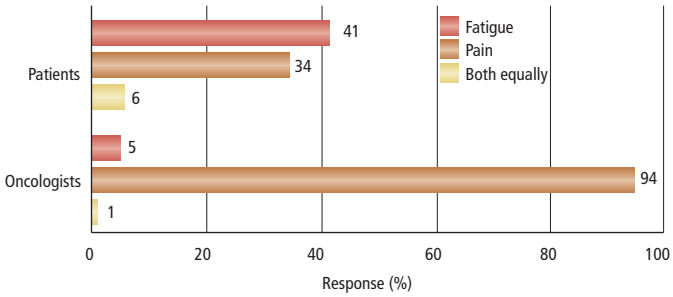
Figure 3: Oncologists' (n=197) and Patients' (n=419) Perception of the Relative Importance of Treating Fatigue or Pain*



*Source: Vogelzang et al., 1997.[14] *In response to the question: "Is/was it more important for pain or fatigue to be reduced or relieved by treatment or are/were both equally important?" Adapted with permission from Elsevier.*

the group of patients who did receive radiotherapy per protocol, no statistically significant differences in disease progression or survival end-points were seen. It should also be noted that both of these studies are inconsistent with the prior literature on these agents and used higher baseline and target Hb concentrations than those approved on-label or in evidence-based guidelines,[35–36] and both utilised off-label doses of rHuEPO. While several studies have demonstrated increased Hb levels, improved QoL and reduced RBC transfusion requirements in anaemic cancer patients following erythropoietic protein therapy[21–25] prospectively designed, long-term studies are required to evaluate the impact of erythropoietic proteins on survival.

Management of Anaemia – The Role of the Oncology Nurse

The oncology nurse is ideally positioned to play a key role in the identification and management of cancer-related anaemia, and to act as a patient advocate. Oncology nurses must proactively and accurately assess cancer-related anaemia and fatigue using appropriate tools and ensure that the information is documented and made available to the rest of the healthcare team. In addition, oncology nurses should: continuously assess and monitor patients; aim to identify signs and symptoms of anaemia early; realise that anaemia is not just a number; evaluate trends in blood profiles over time; implement strategies to prevent and/or reduce the incidence of anaemia; and use evidence-based models to identify patients at risk of developing anaemia.

By accurately anticipating and assessing problems at all stages of treatment, the oncology nurse can be pivotal in reducing the adverse effects of cancer-related anaemia and fatigue. However, to achieve this, the training needs of oncology nurses must be addressed and education on anaemia and fatigue provided. The European Oncology Nursing Society (EONS), in conjunction with the limited liability company (GmbH) Amgen (Europe) have conducted a Learning Needs Assessment (LNA) study in 21 countries involving over 450 nurses. The main objective of this study was to identify the learning requirements of European oncology nurses relating to anaemia, neutropoenia and mucositis. Results of this LNA study have been used to develop the Training Initiative in Thrombocytopenia, Anaemia and Neutropoenia (TITAN) training programme, which is being piloted in Ireland, France and The Netherlands with results expected later this year. The delivery of accurate training programmes specifically tailored for European oncology nurses should improve the prevention, detection and management of haematological toxicities, including anaemia and fatigue, in cancer patients.

Conclusions

Although common in patients with cancer, anaemia is often underdiagnosed and undertreated. Fatigue, which is frequently associated with cancer-related anaemia, has a significant impact on patients' everyday lives. However, cancer-related fatigue appears to be underappreciated by healthcare professionals. Indeed, many patients regard the treatment of fatigue as more important than the treatment of pain, in direct contrast with the opinions of many physicians. Accurate assessment of both anaemia and fatigue is essential if we wish to understand the reality of living with cancer-related anaemia and provide optimal treatment.

Oncology nurses are ideally placed to act as patient advocates and to play a key role in the identification and management of cancer-related anaemia by anticipating and assessing the problem during all stages of treatment. However, cancer-related anaemia is a complex condition with diverse symptoms. Further education on anaemia and fatigue is therefore required and 'needs analyses' for patients and nurses have been conducted in Europe. It is hoped that accurate and detailed training programmes, developed from specific needs analyses, will further enhance the role of oncology nurses. ■

1. Ludwig H, Fritz E, *Semin Oncol*, 1998;25(Suppl. 7):2–6.
2. Groopman JE, Itri LM, *J Natl Cancer Inst*, 1999;91:1616–34.
3. Coiffier B, Guastalla J-P, Pujade-Lauraine E, Bastit P, *Eur J Cancer*, 2001;37:1617–23.
4. Skillings JR, Rogers-Melamed I, Nabholtz J-M, et al., *Eur J Cancer*, 1995;31A(Suppl. 5):S5.
5. Reed WR, Hussey DH, DeGowin RL, *Am J Med Sci*, 1994;308:9–15.
6. Barrett-Lee PJ, Bailey NP, O'Brien MER, Wager E, *Br J Cancer*, 2000;82:93–7.
7. Bokemeyer C, *Elsevier Science BV*, 2001:43–54.
8. Harrison L, Shasha D, Shiaova L, et al., *Semin Oncol*, 2001;28(Suppl. 8):54–9.
9. Mughal T, *Elsevier Science BV*, 15–23.
10. ISIS (2000) Research, Conducted by ISIS Research Ltd. Data on file.
11. Miller CB, Jones RJ, Piantadosi S, et al., *N Engl J Med*, 1990;322:1689–92.
12. Nowrousian MR, *Med Oncol*, 1998;15(Suppl. 1):S19–S28.
13. Cella D, Peterman A, Passik S, et al., *Oncology*, 1998;12:369–77.
14. Vogelzang NJ, Breitbart W, Cella D, et al., *Semin Hematol*, 1997;34(Suppl. 2):4–12.
15. Cella D, *Semin Hematol*, 1997;34(Suppl. 2):13–19.
16. Crawford J, Cella D, Cleeland CS, et al., *Cancer*, 2002;95:888–95.
17. Curt GA, Breitbart W, Cella D, et al., *Oncologist*, 2000;5:353–60.
18. Portenoy RK, Itri LM, *Oncologist*, 1999;4:1–10.
19. Cella D, Eton DT, Lai JS, et al., *J Pain Symptom Manage*, 2002;24:547–61.
20. Houbiers JGA, Busch ORC, Van de Watering LMG, et al., *Eur J Surg*, 1995;161:307–14.
21. Hedenus M, Adriansson M, San Miguel J, et al., *Br J Haematol*, 2003;122:394–403.
22. Littlewood TJ, Bajetta E, Nortier JWR, et al., *J Clin Oncol*, 2001;19:2865–74.
23. Österborg A, Brandberg Y, Molostova V, et al., *J Clin Oncol*, 2002;20:2486–94.
24. Smith RE Jr, Tchekmedyian NS, Chan D, et al., *Br J Cancer*, 2003;88:1851–8.
25. Vansteenkiste J, Pirker R, Massuti B, et al., *J Natl Cancer Inst*, 2002;94:1211–20.
26. Glaspy J, Henry D, Patel R, et al., a randomized study, (abstract 29); 8th International Conference on Geriatric Oncology and the 4th Meeting of the International Society of Geriatric Oncology, Rome, Italy (21–22 November 2003).
27. Caro JJ, Salas M, Ward A, Goss G, *Cancer*, 2001;91:2214–21.
28. Binet JL, Auquier A, Dighiero G, et al., *Cancer*, 1981;48: 198–206.
29. Hasenclever D, Diehl V, *N Engl J Med*, 1998;339:1506–14.
30. Moullet I, Salles G, Ketterer N, et al., *Ann Oncol*, 1998;9: 1109–15.
31. Bohlius JF, Langensiepen S, Schwarzer G, et al., *Blood*, 2003;abstract 709,102:203a.
32. Frommhold H, Guttenberger R, Henke M, *Strahlenther Onkol*, 1998;17(Suppl. 4):31–4.
33. Leyland-Jones B, *Lancet Oncol*, 2003;4:459–60.
34. Henke M, Laszig R, Rübe C, et al., *Lancet*, 2003;362:1255–60.
35. Rizzo JD, Lichtin AE, Woolf SH, et al., *J Clin Oncol*, 2002;20:4083–4107.
www.nccn.org/professionals/physician_gls/PDF/anaemia.pdf
36. Sabbattini P, *Cancer and treatment-related anaemia, version 2*, 14 April 2004.