Abstract. Background: Cancer related anemia impairs patient functioning. Red blood cell (RBC) transfusion and erythropoietin (EPO) may relieve fatigue. Cost-effectiveness data have been requested. Patients and Methods: All transfusions administered at the Department of Oncology, University Hospital of North Norway (UNN) in 2005 were analysed, with a total of 118 patients entering the study. A cost of transfusion analysis was added and a sensitivity analysis conducted to clarify robustness. The 118 patients received 613 units of erythrocytes. In 6% of cases, the transfusion was the only cause of a hospital visit. One fourth of patients had bone marrow infiltration and two-thirds had undergone chemotherapy. The mean Hb levels of patients prior to and following transfusion were in the range 8.4-8.8 g/dl and 10.2-10.6 g/dl, respectively; one-third reached a non-anemic level (Hb≥11.0 g/dl). The median time interval between transfusions was three weeks and the annual cost was calculated at €1,069/patient. Conclusion: RBC-transfusion has a low cost.

Cancer-related anemia is frequently seen as a result of underlying malignancy and/or cancer therapy and a scale to characterise the anemia and treatment recommendations have been developed (1, 2). Two large studies have disclosed that approximately 40% of cancer patients have anemia (3-4). The severity of anaemia varies depending on the malignancy and therapy given and, not surprisingly, impairs patient functioning (5-8). It may even contribute to poor treatment outcomes (9). The treatment of anemia relieves fatigue and may prolong survival by enhancing tumor oxygenation thus increasing its sensitivity to chemotherapy or radiotherapy. Red blood cell (RBC) transfusion, erythropoietin administration or a combination are the main treatment alternatives. Recently, a meta-analysis (10) (9,353 patients) pointed out uncertainties as to whether epoetin may influence overall survival.

In northern Norway, cancer-related anemia is generally treated with RBC transfusion. To explore the health economics in this setting, we analysed all transfusions administered in our unit in 2005.

Patients and Methods

Patients. All patients recorded in the database at the Department of Immunology and transfusion medicine, University Hospital of North Norway (UNN) were retrospectively analysed according to the following selection criteria: The patient had to be treated (in-or out-patient setting) at the Department of Oncology and have undergone at least one RBC transfusion during 2005. A total of 120 patients met these criteria. Of these, one patient was misreported (treated at another department) and another had had the transfusion as backup during surgery, leaving a total of 118 patients entering the final analysis. There were 49 women and 69 males. Most patients suffered from non-Hodgkin’s lymphoma (36 patients), colorectal (21 patients), prostate (14 patients) or breast (13 patients) cancer and their mean age was 64 years (range 17-96 years). Each patient’s place of residence was recorded and the distance to the UNN was calculated employing gulesider’s (www.gulesider.no) travelcalculator. We also registered the main cause for hospital visit/hospitalisation according to two alternatives: i) only erythrocyte transfusion; ii) other causes (in example therapies such as radiotherapy, chemotherapy, hormonal therapy, monoclonal antibodies, treatment of side-effects, or regular check-up according to a follow-up programme). Hb levels prior to and after transfusion were recorded according to the UNN’s electronic patient record folder (Distributed Integrated Patient record System for hospitals – DIPS).

Health economic analysis. Costs were calculated according to the tariff of The National Health Administration (NHA) (11) and the diagnosis-related groups (DRG) system employed in Norway (12). The costs were calculated from the National Health Service’s (NHS) point of view. The following costs were considered: health care costs (C₁), patient/family costs (C₂) and costs in other sectors (C₃).
Health care costs ($C_{j}$). The health care costs include the direct RBC transfusion costs. This includes the charge for blood, associated charges for ancillary laboratory testing necessary for transfusion [measuring of Hb-levels, blood typing (ABO, Rh and antibody screening) and cross matching], and the cost of intravenous line supplies and person-hours of nursing labour associated with the procedures. To reflect the cost of erythrocytes (613 units), the tariff (€165.3/unit) employed when a RBC unit is exchanged between Norwegian hospitals was used. Furthermore costs of hospital stays and out-patient clinic administration need to be implemented. The tariff (11) reflects all cost associated with transfusion (€55.2). The tariff of an outpatient visit (€4.9) was added when RBC transfusion was the only cause of an appointment. When in-patient care was due to RBC transfusion alone, the hospital stay cost (according to the DRG system) combined with blood transfusion (DRG 404, €2,748.6) was employed. When transfusion was performed in addition to in-hospital cancer therapy (chemotherapy, radiotherapy), the tariff (11) employed in an outpatient setting (€55.2) was added as no specific tariff was designated.

The risk of complications and its costs also need to be implemented. This includes infections by human immunodeficiency virus (HIV) (1-2 cases/million transfusions (2)), hepatitis B-virus (HBV) (1/31,000 units transfused (13)) and hepatitis C virus (HCV) (4-10 cases/million transfusions (14)). The costs were calculated as the risk of transmission multiplied by the average cost of managing the illness. The average monthly 2006 cost (€2,754) for acquired immunodeficiency syndrome (AIDS) was employed as a surrogate. A five-year perspective was employed. The annual cost of HBV infection (€4,733) and a worst case scenario where all infections turn from acute to chronic disease requiring 20 years of therapy were implemented in the analysis (€72,528). Furthermore, the cost of an aggressive treatment strategy for HCV infection (€39,467) was added. Details are shown in Table I.

Non-specific febrile reactions to RBC transfusion are common. Conservative management employing antipyretics and/or antihistamines is effective and cheap. Anaphylactic reactions are rare, but serious and have been estimated to occur in 1 in 20,000 to 47,000 transfusions causing 1.52 deaths per million units. In cancer therapy this equates to a reduction in life expectancy related to transfusion of less than a few hours (13, 15). Knowing the potential of adrenaline, steroids and antihistamines in treating severe anaphylactic reactions and the fact that such reactions are very rare, we did not add any costs in this setting.

Patient/family-related costs ($C_{2}$). For practical reasons, the cost of travelling was reflected by the national tariff per kilometre (€0.37) and a median distance of 277 km was used as we had no access to individual transportation data for each patient.

The patient has to cover a small amount (€32.5) of the outpatient clinic costs themselves (11). This figure was included. Hospitalisation is free of charge for patients in Norway.

Costs in other sectors ($C_{3}$). The patients’ median age was 64 years. Most Norwegians retire at the age of 62-67 years. Knowing the overall survival figure and the fact that most patients undergoing cancer therapy are out of the workforce, production losses were excluded from the economic analysis.

Statistical analysis. The Statistical Package for Social Science (SPSS for Windows, SPSS Inc, Chicago, Illinois, U.S.A.) version 13.0 was used to analyse the data. Descriptive statistics was employed. Patients with an unknown value for a particular variable were excluded from analysis involving that variable. Microsoft Office Excel 2003 was employed for the economics calculations and costs were calculated in Norwegian unit costs and converted to Euros (€) at the rate of 1€ = 8.166 NOK as of November 30th 2006. Costs were converted to 2006 values according to Statistics Norway (www.ssb.no). Costs and benefits were discounted employing a 3% discount rate.

Results

Red blood cell transfusions. During 2005, 118 patients were treated with a total of 613 erythrocyte units (U), resulting in an average of 5.2 U/patient. One-third (39/118) underwent at least five transfusions. The number of units transfused at the Department of Oncology constituted 7%
(613/9393) of the total amount of units employed at the UNN. Ten percent (64 units) were administered at the outpatient clinic and 549 transfusions were handled in an inpatient setting. RBC transfusion was usually administered in addition to routine checkups, cancer therapies (radiotherapy, chemotherapy) and extra follow-ups due to side-effects or complications. We found only 17 (6%) occasions where the need for erythrocyte transfusion was the only reason for hospitalisation or out-patient visit. Fifteen of these were handled in an out-patient setting. About one fourth (32 patients) had documented bone marrow infiltration and two-thirds (73 patients) had undergone chemotherapy. Twenty-seven patients died during the study period (12 months), indicating that cancer patients undergoing erythrocyte transfusion often have a poor prognosis.

The mean Hb level pre- and post-transfusion was in the range of 8.4-8.8 g/dl and 10.2-10.6 g/dl, respectively. The median rise in Hb level following transfusions was of 1.7 g/dl. Details can be seen in Figure 1. It is notable that only one third of the patients achieved a non-anemic Hb level (Hb≥11 g/dl) following transfusion. Patients underwent several transfusions with a median time interval of three weeks.

Figure 1. Hb levels before (a) and after (b) the first, second, third and fourth transfusions.
**Health economics.** The total 2005 annual cost of RBC transfusions in cancer-related anemia was indicated at €1,069 per patient. The major cost items were the erythrocyte units (80%) and prolonged hospital stays (12%). A sensitivity analysis (Figure 2) documented the cost of the RBC units as the main factor influencing the results.

**Discussion**

In this study, we have documented the use of RBC transfusions in cancer-related anemia in our unit. Most patients had Hb levels between 8-9 g/dl prior to transfusion and a third achieved a non-anemic Hb-level (≥11 g/dl) following transfusions. The treatment cost of RBC transfusion was low (€1,069 per patient). The blood transfusions constituted 7% of the total figure at UNN.

The use of RBC transfusion or erythropoetin has been heavily discussed during the past few years (10, 16). The two major issues have been whether erythropoietin (EPO) administration may diminish overall patient survival and whether RBC transfusion is the cost-effective approach in this setting. EPO receptors have been recognized in several types of human cancer (17). Studies have demonstrated EPO/EPOR signalling events in cancer cells contributing to disease progression (16). Bohlius and coworkers (10) investigated the overall survival for 8,167 patients from 42 studies and reported a non-statistically significant pooled hazard ration (HR) of 1.08 and raised the possibility that survival may be diminished by EPO. The Breast Cancer Erythropoietin Trial (BEST) study was terminated early due to a higher mortality rate in the EPO group (18).

We have indicated that RBC transfusion has a low cost (€1,069/patient/year), but provides only a short-lived benefit (3 weeks). This figure corresponds well with the cost (US$990, 3.1 U/patient) presented by Kavanagh and colleagues (13). We did not compare the cost of RBC transfusion with the use of EPO. However, several investigators have focused on this topic and concluded that the figure is in favour of transfusion (19-24). Barosi and coworkers (19) ran a model-based cost-effectiveness analysis and their figure for EPO and transfusion were $4,440 and $427, respectively. The cost per quality adjusted life year (QALY) was $189,652 (19). Scheffield and coworkers (24) concluded that 64% of EPO patients responded to therapy at an average cost of $12,971 per patient compared to a 100% response rate for transfusion at only a cost of $4,481. Meadowcroft et al. (22) focused on breast cancer patients and calculated a cost of $169 and $6,483 in the blood transfusion and the EPO arms, respectively. Crèmieux and colleagues (21) calculated sixteen weeks of therapy resulting in a total cost of $7,551 and $1,416 in the EPO and standard care groups, respectively.

Epoetin has been shown to reduce the need for blood transfusions by 17-27% (25-26). Marchetti and Barosi (14) have indicated that 2.6-5.2 patients needed to be treated with
EPO to avoid the transfusion of one unit of blood. Despite this, epoetins have been widely adopted by industrialised countries. The resulting budget impact of epoetins has been calculated at about 10% of the overall direct costs for cancer care and this is expected to continue growing by about 20% each year (14).

The economic burden of epoetins needs to be weighed against the improvement of patients’ quality of life, the potential risk of a negative effect on survival, and patients’ and society’s willingness to pay for a non life-saving therapy. Concerning quality of life, a treatment policy for cancer-related anemia based on RBC transfusion may offer temporary relief to patients with anemia as it stabilises Hb levels, but it cannot prevent deterioration of the quality of life of the anemic cancer patient. This was illustrated by the Hb fluctuations found in our survey. Patients’ willingness to pay was focused on by Ortega and associates (23). The figure was on average $587-$613, while the net incremental treatment cost for the cisplatin and non-cisplatin groups were $2,943 and $3,039, respectively.

Methodological limitations. In our survey, we have focused on a limited time period. It could be argued that the results are only representative for the year 2005. However, knowing the routines of the department for almost twenty years, we would argue that the policy shown here has been held for more than a decade.

When calculating the costs of transfusion therapy in this setting, we had no access to data on RBC transfusions handled by other departments, hospitals, GPs or health care centres. Thus the costs do not represent the costs from society’s point of view.

Conclusion

We conclude that the practice of RBC transfusion in cancer related anemia is justified on clinical and health economic grounds. According to the literature, there may be quality of life improvements in employing EPO, but a possible risk of impaired cancer control and survival have to be taken into account.

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