



## **PHARMAC and erythropoietin for cancer patients**

Associate Professor John Carter and Dr Jennifer Clay recently described the role of erythropoietin for the treatment of anaemia in cancer patients (<http://www.nzma.org.nz/journal/119-1234/1989/>). PHARMAC is currently assessing the cost-effectiveness of widening access to erythropoietin, and we hope that the following observations will help debate.

### **Efficacy and safety of erythropoietin for anaemia associated with cancer treatment**

As Dr Carter and Clay point out, many trials have assessed the efficacy of erythropoietin for chemotherapy-induced anaemia. An updated meta-analysis,<sup>1</sup> based on 57 trials, has reported that treatment with erythropoietin significantly reduced the likelihood of red blood cell (RBC) transfusions by one third and improved haematologic response three-fold.\* However, it is not certain whether erythropoietin improves survival. Two large RCTs have found that erythropoietin-treated patients had significantly worse survival than untreated patients.<sup>2,3</sup> (see endnote †). The meta-analysis<sup>1</sup> commented that uncertainties still remain as to whether erythropoietin affects survival, and the authors caution the use of erythropoietin in combination with thrombogenic chemotherapeutic agents or for cancer patients who are at high risk for thromboembolic events.

Trials are currently underway to further assess the impact of erythropoietin on survival, and until these are available, conclusions cannot be drawn.

### **International guidelines**

The authors refer to the American and British/European guidelines on the use of erythropoietin in cancer.<sup>4,5</sup> The National Institute of Health and Clinical Excellence (NICE)<sup>6</sup> has also produced guidelines on the use of erythropoietin for anaemia induced by cancer treatment. The NICE appraisal committee recommended that erythropoietin not be used for this indication except in the context of ongoing or new clinical trials. It considered that further research is needed to confirm the risks and benefits associated with erythropoietin (specifically mortality), to identify subgroups in whom the possible risks are acceptable, and also the impact of treatment on health-related quality of life.

### **PTAC's recommendation**

The Pharmacology and Therapeutic Advisory Committee (PTAC) considered the efficacy of erythropoietin when used to treat anaemia associated with cancer treatment in February 2006. The Committee noted the increasing body of evidence supporting its use for this indication, including a Cochrane review<sup>7</sup> that indicated that on average patients receiving erythropoietin reduced their transfusion requirements by only one unit of blood.

At this stage, PTAC has recommended no change to the Pharmaceutical Schedule criteria. A copy of the full PTAC minute can be found at [http://www.pharmac.govt.nz/latest\\_PTAC\\_minutes.asp](http://www.pharmac.govt.nz/latest_PTAC_minutes.asp)

## **Cost-effectiveness of erythropoietin**

PHARMAC is currently assessing the cost-effectiveness of erythropoietin compared with blood transfusions for the treatment of anaemia. This analysis will consider any potential cost-savings associated with erythropoietin (such as admission to day procedures units for blood transfusions), and any potential gains in quality of life associated with erythropoietin compared with blood transfusions.<sup>‡</sup>

It should be noted that the US cost-effectiveness analysis referred to by Dr Carter and Clay actually reported a cost per quality-adjusted life year (QALY) of US\$111,000–US\$214,000. In comparison, the cost per QALY of pharmaceuticals funded by PHARMAC within the last five years has generally been less than NZ\$20,000.

## **Hospital Exceptional Circumstances**

The authors refer to the Hospital Exceptional Circumstances (HEC) process, which was established at the request of DHB hospitals to control spending in hospital budgets. HEC allows for the funding of community-based treatments for patients currently in DHB hospitals who are awaiting discharge, where there is no other funding available in the Pharmaceutical Schedule. Funding for HEC is from the DHB hospital's budget. The criterion for funding is that the pharmaceutical must be cost-saving to the hospital. A panel of clinicians considers over 1000 applications each year, with the turnaround time being 48 hours. Further information on HEC can be found on the PHARMAC website at <http://www.pharmac.govt.nz/pdf/ECInfoSheet.pdf>

PHARMAC considers the HEC panel has been consistent in its recommendations regarding erythropoietin (see endnote §). PHARMAC and the HEC Panel are working to improve the clarity of eligibility criteria, and welcome clinicians' direct contact if concerned about consistency.

## **Conclusion**

PHARMAC staff are currently investigating the cost effectiveness of using erythropoietin instead of blood transfusions, and we will keep the sector informed of developments.

Rachel Grocott  
Senior Analyst, Hospital Pharmaceuticals Assessment  
PHARMAC

Scott Metcalfe  
Public Health Physician  
Externally contracted to PHARMAC as Senior Advisor (epidemiology and public health medicine)

Peter Moodie  
Medical Director  
PHARMAC

## Endnotes:

\* Erythropoietin statistically significantly reduced the risk for RBC transfusions (relative risk [RR] = 0.64, 95% CI 0.60 to 0.68; 42 trials with 6510 patients) and improved haematological response (RR = 3.43, 95% CI = 3.07 to 3.84; 22 trials with 4307 patients). However, treatment with erythropoietin increased the risk of thromboembolic events (RR = 1.67 (1.35-2.06); 35 trials with 6769 patients). Erythropoietin's effects on overall survival were uncertain (hazard ratio = 1.08, 95% CI 0.99 to 1.18; 42 trials with 8167 patients).

† Henke et al. (Lancet 2003)<sup>2</sup> reported that among 351 anaemic patients with head and neck cancer undergoing radiotherapy, those who received erythropoietin had a significantly worse overall survival (RR=1.39, p=0.02). The combined endpoint of local/regional tumour progress and death reached by 64.4% of patients receiving erythropoietin and 53.8% of placebo patients (p=0.008). The higher mortality rates in patients receiving erythropoietin was attributed to the high haemoglobin levels (above 14 g/dL in women and 15 g/dL in men), increasing the risk of potentially fatal thromboembolic events (vascular disorders including hypertension, haemorrhage, venous thrombosis, pulmonary embolism and cerebrovascular events, were observed in 11% of patients in the erythropoietin group and in 5% of the placebo group). It was also considered that patients' tumours may have expressed erythropoietin receptors, leading to an effect on tumour growth.<sup>8</sup>

Similarly, the BEST multicentre trial (Lancet Oncol 2003)<sup>3</sup> that investigated the use of erythropoietin as an adjunct to chemotherapy among 939 patients with metastatic breast cancer undergoing first-line therapy was terminated early because survival at 12 months was significantly worse in the group that received erythropoietin than the group that received chemotherapy alone (70% versus 76%; P = .017). The mortality rate during the first 4 months of study was attributed to an increased incidence of thrombotic and vascular events in the erythropoietin group versus control (1% versus 0.2%) and an increase in incidence of disease progression in the erythropoietin group versus control (6% versus 3%).

‡ A wider implication of the funding of erythropoietin is the impact on the cost of blood and blood products in the longer term. This is an issue relevant to the Ministry of Health and DHBs who fund blood transfusion services.

§ To date, the HEC Panel has received twenty-one applications or reapplications requesting the funding of erythropoietin for patients with anaemia who require blood transfusions. A number of these applications have been for patients with chemotherapy-induced anaemia and myelodysplastic syndrome. Nine patients have been recommended for funding (with another case awaiting further information). Most of these patients were unable to receive blood transfusions due to: intolerance to desferrioxamine (treatment for iron overload); development of multiple antibodies resulting in inability to transfuse RBCs; poor venous access; or rare blood group and persistent anaemia despite transfusion.

Eight of the eleven cases that were not recommended for funding were patients who had personal or religious objections to receiving blood transfusions or blood products, rather than clinical need. In these cases, blood transfusions were fully funded alternatives that would have been less costly for hospitals. Patients not wishing to use the funded alternative have the option to self-fund or seek funding from elsewhere. The other three patients (two with ribavirin-induced anaemia, one with myelodysplasia) were not recommended for funding because the panel considered there would not be savings to hospital budgets.

## References:

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