Oprelvekin: a review of its pharmacology and therapeutic potential in chemotherapy-induced thrombocytopenia

Wilde M I, Faulds D

Authors' objectives
To assess the efficacy of oprelvekin in chemotherapy-induced thrombocytopenia.

Searching
The authors searched the electronic MEDLINE and AdisBASE databases (1966 to June 26, 1997) for publications in any language using the search terms: 'oprelvekin', 'interleuken-11', 'II-11', 'RHIL-11', 'YM-294', 'recombinant human interleuken-11' and 'thrombocytopenia'. The authors also scanned the reference lists of retrieved articles for additional relevant studies.

Study selection
Study designs of evaluations included in the review
Placebo-controlled phase II trials and dose-finding studies.

Specific interventions included in the review
Oprelvekin administered subcutaneously before and/or after chemotherapy in dose-finding studies and oprelvekin administered subcutaneously after chemotherapy in placebo-controlled trials (25 or 50 micrograms/kg/day once daily for up to 21 days after chemotherapy). Patients also received concomitant granulocyte colony-stimulating factor (G-CSF).

Participants included in the review
Patients undergoing chemotherapy for various forms of cancer (predominantly women with breast cancer, some patients had other solid tumours or lymphoma) for the first time or who had undergone previous chemotherapy. Patients were included if they had not previously received platelet transfusions or had received a platelet transfusion for severe chemotherapy-induced thrombocytopenia in the previous chemotherapy cycle.

Outcomes assessed in the review
Requirements for platelet transfusions, time to platelet recovery, effects on median nadir platelet counts and mean increases in platelet counts.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
No formal assessment of quality was undertaken.

Data extraction
The authors do not state who, or how many of the authors, performed the data extraction. Data were extracted for the categories of: study reference, patient characteristics and trial design, treatment regimen (number of evaluable patients), mean time to recovery of platelet counts to more than 20,000, more than 50,000, and more than 100,000/microlitres, respectively (days), median duration of platelet counts of more than 20,000, more than 50,000, and more than 100,000/microlitres, respectively (days), requirement for platelet transfusion (patients not requiring transfusion (%) and number of transfusions required), time to maximum platelet counts, and median nadir platelet count.
Methods of synthesis
How were the studies combined?
The studies were combined in a narrative review which reported individual study doses and outcomes.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

Results of the review
Three randomised phase II placebo-controlled trials which each had 75 to 82 patients (n = 206), and 2 dose-finding studies with 30 patients in the intervention group with 20 historical controls.

In the dose-related trials (2 trials) oprelvekin shows a trend towards a shorter time to maximum platelet counts with dosages of 50 and 75 micrograms/kg/day versus 10 and 25 microgram/kg/day and a lower requirement for platelet transfusions was observed with dosages of 25 and 75 micrograms/kg/day versus 10 microgram/kg/day. Dosages of 25 and greater microgram/kg/day also appear to reduce the severity of chemotherapy-induced thrombocytopenia compared with 10 microgram/kg/day. However, dosages of 75 or greater microgram/kg/day were associated with an increased incidence of grade 2 adverse events. The combination of oprelvekin and G-CSF appears to accelerate platelet recovery compared with G-CSF alone (statistical analysis not reported).

In the placebo-controlled trials (3 trials) significantly fewer oprelvekin 50 microgram/kg/day than placebo recipients required platelet transfusions and there was a trend towards a lower number of platelet transfusions required with oprelvekin. There was also a trend towards less time to platelet recovery with oprelvekin and improved platelet nadirs compared with placebo, reaching statistical significance in cycle 2 of 1 study. Oprelvekin appears to be effective irrespective of previous platelet transfusion or chemotherapy regimens. Oprelvekin had no effects on myeloid or erythroid cell lineages. In particular, oprelvekin did not ameliorate chemotherapy-induced leucopenia or neutropenia and had no effects on time to neutrophil engraftment or red blood cell transfusion requirements.

Most oprelvekin recipients had increases in C-reactive protein and other acute phase proteins.

One preliminary phase I/II study of 5 children (ages 10 months to 26 years) found oprelvekin 50 microgram/kg/day plus G-CSF reduced the median number of platelet transfusions (2 versus 12) and the median platelet recovery time (19 versus 27 days) compared with G-CSF alone (historical group).

The most common adverse events reported with oprelvekin (oedema and dyspnoea) were dose-related: Oprelvekin 10, 25 and 50 microgram/kg/day were well tolerated, whereas doses > or equal to 75 microgram/kg/day were associated with grade 2 fatigue and myalgia/arthritis, atrial arrhythmias and fluid retention. Other than a higher incidence of severe asthenia with oprelvekin than with placebo (14% versus 3%) the incidence of severe or life-threatening adverse events was similar between treatments. The most common laboratory abnormality with oprelvekin reported in clinical trials was a decrease in haemoglobin levels (causing mild anaemia) and haematocrit values (by approximately 20%).

Authors' conclusions
Oprelvekin is the first pharmacological agent to become available for use in patients with nonmyeloid malignancies and severe cancer chemotherapy-induced thrombocytopenia. Clinical evidence suggests that the drug accelerates platelet recovery, reducing the need for platelet transfusions and reducing severe thrombocytopenia.

CRD commentary
The authors have clearly stated their research question and some inclusion and exclusion criteria. The literature search is limited and the authors may have missed studies published outside the United States by restricting the searches to the two databases and only English language publications.

The quality of the included studies was not formally assessed and the authors have not reported on how the articles were selected, or how many of the reviewers were involved in the data selection and extraction.
The data extraction is reported in tables and text and a narrative pooling was appropriate due to the many differences between studies. There were no tests for heterogeneity and the authors have not discussed the review's methodological or data limitations.

The authors' conclusions appear to follow from the results but should be viewed with caution because of the methodological limitations of the review.

**Implications of the review for practice and research**

Practice: The authors state the recommended dosage and treatment regimen for oprelvekin and give guidelines for the management of patients' adverse events.

Research: The authors state that studies assessing the efficacy of oprelvekin in patients receiving chemotherapy regimens of > 5 days' duration or regimens associated with delayed myelosuppression are required. The authors also state that further studies are needed to determine whether oprelvekin accelerates platelet recovery. A Phase III RCT comparing oprelvekin plus G-CSF with G-CSF alone in children is needed.

**Bibliographic details**


**PubMedID**

18020592

**Indexing Status**

Subject indexing assigned by NLM

**AccessionNumber**

11998001457

**Date bibliographic record published**

30/09/2000

**Date abstract record published**

30/09/2000

**Record Status**

This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.