The efficacy of arsenic trioxide for the treatment of relapsed and refractory multiple myeloma: a systematic review

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CRD summary
This review concluded that the potential efficacy of arsenic trioxide in refractory multiple myeloma was demonstrated, but the validity of the findings was reduced by considerable methodological flaws. In spite of some possible flaws in the review process these conclusions appeared appropriate and are likely to be reliable.

Authors’ objectives
To evaluate the effect of arsenic trioxide (ATO) on multiple myeloma in adults who required systemic treatment for relapsed or refractory disease.

Searching
PubMed, EMBASE, Web of Science and The Cochrane Library were searched from inception to November 2008 (search terms were reported) for studies published in English. Reference lists and abstracts from the most recent meeting of American Society of Hematology (2007) were also searched.

Study selection
Randomised controlled trials (RCTs), cohort studies, case-control studies and case series of adult patients who suffered from multiple myeloma (progressive stadium II or III according to the Salmon and Durie classification) that used ATO containing therapy regimes were eligible for inclusion. Patients had to have relapsed from standard first-line therapy or be refractory to chemotherapy. Eligible outcomes were overall response rates (complete remission plus partial remission plus minimal response), probabilities for overall survival and progression free survival with odds ratios (ORs) or risk ratios (RRs) where applicable.

The included studies were published between 2002 and 2008. Most were conducted in developed countries. The median age of included participants ranged from 54 to 66 years where reported. Treatment regimens varied in dosage (ATO dosage ranged from 0.125 to 0.3mg/kg/day) and combinations used. All of the included studies had a primary outcome of change in the amount of serum monoclonal protein as the main measure of response rate. Two studies included previously untreated myeloma patients.

The authors stated neither how studies were selected nor how many reviewers were involved in study selection.

Assessment of study quality
Methodological quality was assessed using a validated checklist in terms of aims, reporting of number of patients, response criteria, inclusion criteria, randomisation, blinding and similarity of groups at baseline. The level of evidence was determined using the SIGN Guidelines.

The authors did not report how many reviewers were involved in validity assessment.

Data extraction
Complete remission, partial remission, minimal response, stable disease and progressive disease rates and ORs were calculated for each study if data were available.

The authors did not state how many reviewers extracted the data.

Methods of synthesis
The studies were synthesised narratively and presented by ATO as a single agent or combined with ascorbic acid, ATO.
as part of a combined cytostatic regimen and ATO in the RCT.

Results of the review
Sixteen studies were included in the review (n=315, range 4 to 65): 15 case series (n=267) and one RCT (n=48). One case series was excluded from the analysis due to lack of data. Fifteen studies were quality assessed: all studies had clearly formulated aims and descriptions of the interventions and clearly reported numbers of responding patients and the overall number. Response criteria were not reported in five studies. Patient selection was unclear in all studies and information on randomisation and blinding was not available. Six studies (including the RCT) were only reported as abstracts.

In the five case series of ATO as a single agent or in combination with ascorbic acid (n=73) partial remission rates ranged from 0% to 17%. No complete remissions were reported.

In the 10 case series that used ATO in addition to dexamethasone, melphalan or other cytostatic agents, overall response rates ranged from 12% to 100%. Complete remissions ranged from 0 to 25%. The duration of responses ranged from 0 to 24 months.

The one RCT was a three-armed trial (ATO with melphalan in one arm and two arms that added additional ATO in different dosages). There was no significant difference in response rates and survival between treatment arms.

Authors’ conclusions
The results demonstrated the potential efficacy of ATO in refractory multiple myeloma, but the validity of the findings was reduced by considerable methodological flaws.

CRD commentary
The review question was supported by clear inclusion criteria. Four relevant databases were searched, but the search was limited to studies published in English and so publication and language biases could not be ruled out. The review processes were not described, so it was unknown whether measures to reduce reviewer error and bias (such as performing processes in duplicate) were used. It appeared that study validity was assessed using appropriate criteria. The poor study quality and weak study designs were taken into consideration in the analysis. A narrative synthesis appeared appropriate in the presence of considerable clinical heterogeneity. In spite of some possible flaws in the review process the authors’ conclusions appeared appropriate and are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that there was no role for ATO in the routine clinical management of multiple myeloma.

Research: The authors stated that further RCTs that investigated ATOs or new arsenicals were needed. Outcome measures should also include patient-relevant measures such as overall survival and progression-free survival.

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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.