Medical treatment of advanced testicular cancer
Feldman D R, Bosl G J, Sheinfeld J, Motzer R J

CRD summary
The review concluded that favourable outcomes for advanced testicular cancer have been achieved through accurate risk stratification and well-designed trials of risk-tailored therapy. Some patients refractory to initial treatment can be cured with second- or third-line salvage therapy. Limitations of the review and the poor reporting of review methods mean that these conclusions may not be reliable.

Authors' objectives
To review the efficacy and safety (long- and short-term complications) of treatments used for advanced testicular germ cell tumours (GCTs).

Searching
MEDLINE and the Cochrane CENTRAL Register were searched for English language publications from inception to October 2007; the search terms were reported. The references of relevant articles were also checked.

Study selection
Randomised controlled trials (RCTs), meta-analyses, phase 2 clinical trials and large retrospective series (with at least 20 participants) of treatment for advanced testicular GCT were eligible for inclusion. Case reports other than those describing chemotherapy-related toxicity of late relapse were excluded, as were non-randomised trials of first-line treatment regimens. Studies of tumours metastatic to the testes or localised testicular cancer were not eligible for inclusion. Studies focusing solely on children and women were also excluded. Most of the first-line treatment regimens included two or three drug combinations based on bleomycin, etoposide, cisplatin and ifosfamide for 3 to 4 cycles. The authors did not state any inclusion criteria for the outcomes, however, they reported that they excluded 65 studies for not reporting the outcome of interest.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The validity of the RCTs was assessed using the Jadad scale. The authors did not state that they assessed the validity of other study designs, nor did they state how many reviewers performed the validity assessment.

Data extraction
The participants were categorised as good, intermediate or poor prognosis according to the Prognostic Risk Classification of the International Germ Cell Cancer Collaborative Group.

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
The studies were combined in a narrative, grouped by risk stratification (good, intermediate or poor prognosis) or outcome.

Results of the review
One hundred and eighty-five studies (number of participants not reported) were included in the review. There were 68 studies on chemotherapy regimens, including first-line treatment (24 RCTs), second-line treatment (2 RCTs, 12 prospective phase 2 studies, 6 retrospective studies and 1 retrospective matched pair study) and post chemotherapy surgery (22 retrospective studies); 17 studies on late relapse (retrospective series); and 104 studies on toxic effects (4 RCTs and 100 retrospective series).
In the initial management of metastatic GCT, approximately 90% of patients classified as having good prognosis achieved a complete remission to either 4 cycles of etoposide and cisplatin or 3 cycles of cisplatin, etoposide and bleomycin. Complete response was less frequent in patients with intermediate- and poor-risk (55 to 82%) GCTs with standard care comprising 4 cycles of bleomycin, etoposide, and cisplatin.

Second- and third-line treatment regimens were also found to have curative potential. Successful approaches included either standard doses of 3-drug combinations based on ifosfamide and cisplatin or high-dose chemotherapy with autologous stem-cell support. Durable response rates with conventionally dosed salvage regimens (e.g. ifosfamide and cisplatin plus either vinblastine or etoposide) ranged from 7 to 26%. A durable response rate of 63% was found for the combination of paclitaxel, ifosfamide and cisplatin, with a median follow-up of 69 months. Limited data exist to guide the choice of high-dose or conventional-dose chemotherapy for initial salvage treatment; one prospective trial found no significant difference in 3-year event-free and overall survival between the two approaches, while one retrospective study found a 10% benefit in 2-year disease-free and overall survival with high-dose therapy.

A 2 to 6% incidence rate of 'late relapse' (relapse, in the absence of a second primary testicular cancer, at least 2 years after treatment completion) was found. The majority of late relapses occur more than 5 years (median 5 to 10 years) following the completion of treatment, with the latest relapse occurring 32 years after treatment completion.

Acute toxicities associated with the most commonly used chemotherapy treatments of GCT include myelosuppression leading to febrile neutropenia, bleeding and anaemia. GCT chemotherapy has also been linked to acute cardiovascular and thromboembolic events. Acute adverse events of bleomycin included pulmonary toxicity and Raynaud phenomenon. Select toxic effects of other chemotherapy drugs used to treat GCT were also reported. Chronic toxicity associated with treatment included cardiovascular disease, infertility and secondary malignancies.

**Authors' conclusions**

Favourable outcomes for advanced testicular cancer have been achieved through accurate risk stratification and well-designed sequential trials of risk-tailored therapy. Some patients who are refractory to initial treatment can still be cured with second- or third-line salvage therapy with either ifosfamide-based regimens or high-dose chemotherapy with autologous stem-cell support. Clinicians should be familiar with the potential long-term complications of these therapies.

**CRD commentary**

The review question was broad and this was reflected in the inclusion criteria reported. Two relevant databases were searched, but the search was limited to studies published in English and no attempt was made to locate unpublished material. As such, it is possible that relevant studies were missed and the review may be subject to language and publication bias. The methods used to select papers for inclusion in the review, assess study validity and extract the data were not reported. Methodological quality was only assessed for RCTs and the results were not reported. Some details of some of the studies were tabulated, but further details about the participants and regimens in the included studies would have helped determine the generalisability of the results. The authors appear to have only discussed a selection of the included studies. Uncertain quality of the included studies, lack of study details and lack of reporting of review methods limit interpretation of the results presented and, as such, the authors' conclusions may not be reliable.

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

**Practice:** The authors stated that physicians should be aware of the potential long-term complications of treatment for GCTs.

**Research:** The authors stated that in order to improve on current treatment options, future research should focus on recognising and minimising late toxicities of the therapy and enhancing the genetic and biologic understanding of GCTs.

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