A literature review of single agent treatment of multiply relapsed aggressive non-Hodgkin's lymphoma
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Authors' objectives
To assess the effectiveness of single-agent chemotherapy regimens in multiply relapsed aggressive non-Hodgkin's lymphoma.

Searching
MEDLINE (from 1966 to 2001) and EMBASE (from 1974 to 2001) were searched using the keywords reported in the review. The authors also searched the proceedings of annual meetings of the American Society of Hematology and the American Society of Clinical Oncology (1994 to 2001) for additional studies.

Study selection
Study designs of evaluations included in the review
Prospective studies that described both treatment and outcomes were eligible for inclusion. The authors included stage I and II studies, most of which aimed to identify agents that would have palliative benefits and which could also be used in novel primary and salvage combinations. None of the studies included in the review appears to have had a comparator (control). The studies focused on response rates, rather than comparing the effectiveness of various single-agent regimens, or the effectiveness of single-agent chemotherapy versus another treatment option.

Specific interventions included in the review
Studies of any single-agent chemotherapy regimen were eligible for inclusion. Studies of the following agents were included: 9-aminocamptothecin, anti-B4-bR, Ara-C, bisantrene, cladribine, demethoxydaunorubicin, etoposide, fludarabine, gemcitabine, idarubicin, rituximab, ibritumomab, ifosfamide, interleukin 2, I-131-tositumomab, mitoxantrone, oxaliplatin, paclitaxel, topotecan, trofosfamide, vincristine, vincristine liposomal and vinorelbine. The authors did not report the exact doses or duration of treatment.

Participants included in the review
Studies that included three or more people with multiply relapsed (second or later relapse) aggressive non-Hodgkin's lymphoma were eligible for inclusion. The authors noted that many trials included patients with a variety of non-Hodgkin's lymphoma histological and immunohistological subtypes, but did not present the results for these groups separately. The authors did not report characteristics of the participants such as age or gender.

Outcomes assessed in the review
The authors did not specify any inclusion and exclusion criteria for outcomes in the primary studies. It appears that prospective studies reporting any outcome were considered for inclusion. The outcomes reported in the review were response to treatment (complete plus partial response) and toxicity, measured as per the primary studies.

How were decisions on the relevance of primary studies made?
Two authors screened the abstracts of identified studies to assess whether they fulfilled the inclusion criteria. Studies including three or more people at initial presentation or first, second, or later relapse, were selected for further examination. Only reports of people with second or greater relapse were included in the final review. A third reviewer checked the selections.

Assessment of study quality
The authors did not state that they assessed validity.
Data extraction
The authors did not report how the data were extracted for the review, or how many reviewers performed the data extraction. The authors reported that they extracted data on study design, number of centres, drug dose and schedule, patient characteristics, study end points, responses, the method used to evaluate response, toxicities and study power. Only data on response and toxicities were presented in the review.

Methods of synthesis
How were the studies combined?
The authors tabulated the main outcomes and provided a narrative overview of the main trends.

How were differences between studies investigated?
The authors described differences between the studies to some extent, but did not report a formal method for assessing differences between the studies.

Results of the review
The authors identified 36 phase I and II studies of 23 different chemotherapy agents. Most were single-centre studies. The authors reported the number of patients where response was evaluable in each study, rather than the total number of participants recruited. The number of evaluable patients ranged between 3 and 100 people per study (total 693, where reported).

Response.
The reported response rates ranged from 0 to 67%. The median duration of response was about 6 months. Etoposide, vincristine, vinorelbine and rituximab were the only single agents associated consistently with a response rate greater than 30%. Of the studies reporting response rates of 30% or more, all but four were based on fewer than 20 participants (some as few as 6). The authors did not report the confidence intervals for response rates.

Toxicity.
The authors tabulated the proportion of participants with various toxicities for each of the single-agent regimens. Most single agents were associated with significant myelotoxicity. Rituximab had fewer grade 3 or 4 adverse effects compared with some other agents, although studies of rituximab included small samples. Paclitaxel and vinca alkaloids were most likely to be associated with neurotoxicity.

Authors' conclusions
There is currently no accepted standard therapy in multiply relapsed aggressive non-Hodgkin’s lymphoma. Only etoposide, vincristine, vinorelbine and possibly rituximab appear to have a response rate greater than 30% (complete plus partial response). However, the majority of the studies were small and uncontrolled, and of limited quality.

CRD commentary
The authors addressed a defined research question and specified their inclusion and exclusion criteria clearly. The search strategy was limited to two English language databases and the proceedings of two meetings, so some relevant studies might have been excluded. It was unclear whether there were any language restrictions. The authors did not assess whether publication bias or language bias may have impacted on the findings of the review.

The authors did not report any formal methods for assessing the validity of studies included in the review, although they did acknowledge the poor quality of the primary studies. Although data on study characteristics and participant demographics were extracted, such data were not presented in the review, nor were the doses or timing of treatment regimens described. This lack of detail limits the review significantly. The lack of data on the characteristics of the participants also makes it difficult to generalise the findings to specific patient sub-populations.

The authors acknowledge difficulties in extracting data for the analysis. For example, some studies were completed
before the Working Formulation or the Revised European American Lymphoma (REAL) classification of non-Hodgkin's lymphoma were implemented. This means that the proportion of participants with a specific histological subtype could not always be determined accurately. Many studies included patients with a variety of histological and immunohistological subtypes of non-Hodgkin's lymphoma who had received one or more prior treatments, but did not report the results for these groups separately. The authors did not report the confidence intervals for response rates, but in small studies these would have been wide. A narrative synthesis seems to have been appropriate given the variation between the studies, however, the synthesis was lacking in detail. The authors could have synthesised the data more fully and provided more details of the individual studies to help the reader assess the validity of the conclusions.

The authors addressed an important topic, but the results of the review are of limited use for clinical practice. Conclusions about the most effective drug or dose for multiply relapsed aggressive non-Hodgkin's lymphoma cannot be drawn from the findings of this review.

Implications of the review for practice and research
Practice: The authors did not state any explicit implications for practice.

Research: The authors stated that further large trials with more rigorous reporting are needed to assess the relative benefits of single-agent chemotherapies. They recommended that investigators provide more details about patient characteristics, prior treatments, and end points other than simple response rates.

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