Role of chemotherapy and rituximab for treatment of posttransplant lymphoproliferative disorder in solid organ transplantation

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CRD summary
This review concluded, from limited evidence, that overall response rates for rituximab and/or chemotherapy for post-transplant lymphoproliferative disorder treatment after solid organ transplantation ranged from 50 to 100% and five-year survival was 60%. The authors’ cautious conclusions appear to reflect the limited quantity and quality of the data, but their reliability is difficult to assess due to poor reporting.

Authors' objectives
To assess the role of chemotherapy and/or rituximab for the treatment of post-transplant lymphoproliferative disorder after the transplantation of solid organs.

Searching
MEDLINE was searched from 1966 to May 2007. Search terms were reported. The references of relative articles and recent abstracts (2004 to May 2007) from haematology, oncology and transplantation scientific meetings were also screened.

Study selection
Prospective studies, retrospective studies and case series reporting clinical data on the use of rituximab and/or chemotherapy for the treatment of post-transplant lymphoproliferative disorder, in patients having undergone solid tissue transplantation, were eligible for inclusion.

Roughly equal numbers of included studies assessed rituximab alone (375 milligrams per metre-squared (mg/m²) per dose per week) and chemotherapy alone (various regimens), for second-line therapy. The remaining studies assessed combination therapies. All of the included patients had their immunosuppressive therapy reduced either before or during the treatment period of the trials, as a first-line treatment. Median age of included patients ranged from four to 58 years and Epstein-Barr virus positivity ranged from 29 to 100%. The most common types of transplant were kidney, liver, heart and lung. The median time from transplantation to post-transplant lymphoproliferative disorder onset ranged from seven to 85 months, with a predominance of monomorphic histological findings. The most commonly reported outcomes were response rate (overall or complete) and survival. Adverse events were reported in most studies.

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

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Percentage response and adverse events rates were extracted. Median time durations were reported for time to event data such as survival.

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

Methods of synthesis
Studies were combined in a narrative synthesis according to the intervention type.

Results of the review
Sixteen studies were included in the review; six prospective studies (n=138 patients), nine retrospective studies (n=388
patients) and one pilot study (n=9 patients). Sample sizes ranged from 9 to 193 patients, with most studies having less than 35 participants.

**Rituximab as second-line therapy** (n=114 patients, five studies): Two retrospective studies and three prospective studies assessed rituximab monotherapy for second-line treatment, with response rates ranging from 44 to 64%. The largest prospective study reported a median survival of 15 months and an overall response rate of 68% at one year after treatment.

**Chemotherapy as second-line therapy** (n=307 patients, six studies): One prospective study, four retrospective studies and one pilot study assessed chemotherapy alone for second-line treatment, with response rates ranging from 25% to 83%. The prospective study was small and reported the largest overall response rate (83%).

**Rituximab plus chemotherapy as second-line therapy** (n=66 patients, three studies): Two prospective and one retrospective study assessed chemotherapy combined with rituximab for second-line therapy. Both prospective studies reported high overall response rates of 83% and 100%, whilst the retrospective trial reported a response rate of 68%, increasing to 74% 27 months after treatment.

**First-line therapy comparisons** (n=65): Three studies, all small retrospective studies, assessed chemotherapy alone, rituximab alone or a combination of therapies for first-line therapy. Overall response rates were similar to those reported previously.

**Adverse events**: Serious adverse events were more frequently reported for chemotherapy as compared to rituximab and ranged from grade 3 neutropenia to infection resulting in death.

Where available data relating to complete response rates and survival were also reported in the review.

**Authors' conclusions**
Limited evidence from prospective and some long-term retrospective follow-up studies suggested that overall response rates ranged from 50 to 100% and five-year survival after therapy was 60%. There was no evidence to determine the relative effectiveness of the different types of treatment.

**CRD commentary**
This review answered a research question, which lacked clarity in terms of outcome and intervention: study design was also broadly defined. Only one database was searched for studies. Although other sources were searched, there may be a risk that some relevant data may have been missed. The reliability of the review process was also unclear, as the authors did not report their methods. The lack of assessment of study quality made it difficult to assess the reliability of the review data. There was a lack of large comparative prospective studies and the overall quality of the data appeared to be poor, although the authors did make recommendations for further research. A narrative synthesis seemed appropriate given the variation in important prognostic factors, differences in study design and patient populations. Overall, the authors' cautious conclusions appear to take into account the limited quantity and quality of the data, but it is difficult to assess their reliability, given the poor search and limited description of the review process.

**Implications of the review for practice and research**
**Practice**: The authors stated that treatment strategies for post-transplant lymphoproliferative disorder need to be individualised according to Epstein-Barr virus status, histology, aggressiveness, onset of disease and IPI scores. Rituximab monotherapy may be initiated in Epstein-Barr virus-positive patients and early-onset post-transplant lymphoproliferative disorder. Chemotherapy may be reserved for those patients who are refractory to rituximab. A combination of both treatments should be considered for those patients with CD20+ monomorphic or high grade post-transplant lymphoproliferative disorders at the time of diagnosis, regardless of their Epstein-Barr virus status. In this high risk population, granulocyte colony-stimulating factors and antibiotics should also be considered to help reduce infectious complications and mortality related to chemotherapy.

**Research**: The authors stated that further prospective comparative studies are urgently required to confirm the effectiveness of second-line treatment with rituximab and/or chemotherapy for post-transplant lymphoproliferative disorder after solid organ transplantation. Such trials should also assess effects in different subgroups of patients.
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