APPENDIX 3C: CRITICAL APPRAISAL OF TOPIC

Topic: Treatment of warm autoimmune hemolytic anemia secondary to chronic lymphocytic leukemia	**Date completed: 8/30/16**

Clinical Problem: A 65 year old caucasian woman with h/o squamous cell carcinoma, myocardial infarction s/p stent and chronic lymphocytic leukemia (CLL) who presents for management of her warm autoimmune hemolytic anemia secondary (wAIHA) to CLL. She has symptoms of dark urine. Her hemoglobin has fallen below 10 g/dL, her haptoglobin has decreased and her mean corpuscular volume, reticulocyte count, and serum lactate dehydrogenase have increased despite treatment with rituximab. She had a sustained response with prior treatment of her AIHA with prednisone however prednisone was discontinued to avoid the side effects of increasing dosage of maintenance therapy.

Structured Question:

Population/problem: In an elderly patient with wAIHA secondary to CLL that no longer responds to rituximab therapy

Intervention: Low dose Prednisolone (a metabolite of prednisone)

Comparison: Prednisolone-Rituximab combination therapy

Outcome: Complete response or increased relapsed free survival

Type of question:
☒Therapy/Prevention ☐ Diagnosis ☐ Prognosis ☐ Etiology/Harm ☐ Cost analysis

Ideal type of study:
☒RCT ☐ Meta-Analysis ☐ Practice Guideline
☐ Cohort Study ☐ Systematic Review ☐ Case Series/Case Report/Case Control

Citation/Reference (e.g., author(s); article title; journal; volume/issue/pages; year):
Randomized Control Trial:

1. Birgens, H., Frederiksen, H., Hasselbalch, H. C., Rasmussen, I. H., Nielsen, O. J., Kjeldsen, L., . . . Schöllkopf, C. (2013). A phase III randomized trial comparing glucocorticoid monotherapy versus glucocorticoid and rituximab in patients with autoimmune haemolytic anaemia. *British Journal of Haematology Br J Haematol, 163*(3), 393-399. doi:10.1111/bjh.12541

Type of Study:
A randomized control trial was used to answer this question.

Resources (e.g., Cochrane; PubMed) and Search Terms:

- Pubmed, search terms: Autoimmune hemolytic anemia treatment, rituximab, prednisone
- Cochrane library, search terms: Autoimmune hemolytic anemia

Summary of Evidence:

Is the study valid? [explain]

- 2013 Randomized Control Trial

  This study is valid. Assignments were randomized and concealed. Eligible patients were randomized 1:1 by use of pre-coded envelopes.

  This study is valid. All patients were analyzed to the groups which they were randomized to. It allowed for the comparison of the intervention group (Rituximab and Prednisone) and control group (Prednisone only), and included methodologies to reduce the potential for bias. A total of 65 patients were initially allocated to either of thetwo treatment groups, but one patient withdrew informedconsent and was removed from the study. Thus 32 patients were randomized to prednisolone and 32 to a combination of prednisolone and rituximab. There were no statistically significant differences between the two groups with respect to age, sex ratio, hemolytic activity, liver and renal function, or the proportion with an underlying lymphoproliferative or autoimmune disease.

  This study is valid. The groups were treated equally apart from the experimental treatment. All patients received prednisolone 1.5 mg/kg/d for 2 weeks followed by tapering according to this schedule: 0.75 mg/kg/d for 1 week (week 3), thereafter 0.5 mg/kg/d for 1 week (week 4), followed by a gradual reduction over the next 4–8 weeks to the lowest dose that was effective in maintaining a normal hemoglobin level. In the group allocated to a combination of prednisolone and rituximab, the patients received prednisolone at the same dose and schedule as in the monotherapy group and were given rituximab at a dosage of 375 mg/m2 as an intravenous infusion once a week for 4 weeks. All patients received oral folic acid 5 mg/day, and those given a rituximab infusion also received premedication with acetaminophen 1 g and clemastine 2 mg intravenously 30–60 min before the infusion. The patients underwent a full clinical examination and complete blood counts including hemolytic parameters at enrollment, on days +7, +14, +21, +28, +42, +56, +70 and +84, then monthly until month 6, and finally, every third month until the end of follow-up. This applied to all patients until they showed a lack of response necessitating either a switch to some other immunosuppressive treatment or splenectomy, or they relapsed after an initial positive response.

  This study is valid. Follow up was sufficiently long and complete. Response to treatment was evaluated at 3, 6, 12 months in the interventions and control groups however the minimum and maximum follow-up times after initiating treatment were 12 and 48 months, respectively.

  Patient and clinicians were not kept blind to treatment.

What are the results?
▪ Clinical effect

- 2013 Randomized Control Trial

  The primary objective of the study was to analyse differences in treatment responses between the two groups. Responses were evaluated at 3, 6 and 12 months after treatment was initiated. Complete response (CR) was defined as normalization in hemoglobin concentration without any ongoing immunosuppressive treatment and without any biochemical signs of hemolytic activity. Partial response (PR) was defined as being similar to CR but requiring continued low-dose prednisolone (<10 mg/day), or appearing as compensated hemolytic anaemia entailing a stable, acceptable hemoglobin level without any need of treatment except < 10 mg/day prednisone.

  Secondary objectives of the investigation were to evaluate differences in relapse-free survival, red blood cell transfusion requirement after treatment, and the need for splenectomy.

  The data showed that using rituximab and prednisolone combined rather than prednisolone alone as first-line treatment in wAIHA increases both the rate and the duration of the response. The relapse free survival in all responders was significantly higher in the patients receiving rituximab and prednisolone combined. Thirty-six months after start of treatment, about 70% of the patients who showed either CR or PR were still relapse-free in the combination treatment group, whereas the corresponding proportion in the group receiving prednisolone monotherapy was only about 45%. With respect to red blood transfusion, there was was no difference between the prednisolone/rituximab group and the prednisolone monotherapy group when comparing responders (total and partial) from enrollment to end of response or to the end of study follow-up. The number of patients that underwent splenectomy due to relapse or lack of response was essentially equivalent in the two treatment groups (4 in the rituximab group and 3 in the non-rituximab group).There was no significant difference between the two groups regarding adverse reactions to the studied medications. Likewise, serious adverse events were equally distributed, and no allergic reactions to rituximab were recorded.

▪ Precision & statistical

- 2013 Randomized Control Trial

  After 12 months, a satisfactory response was observed in 75% of the patients treated with rituximab and prednisolone but in a significantly smaller proportion (36%) of those given prednisolone alone (P = 0.003). Furthermore, relapse-free survival was significantly better after the combined therapy than after prednisolone monotherapy. After 36 months, about 70% of the patients were still in remission in the rituximab-prednisolone group, whereas only about 45% were still in complete or partial remission in the prednisolone group (P = 0.02).

  Control Event Rate (Prednisone monotherapy) at 12 months = 74% (occurrence of wAIHA)
  Experimental Event Rate (Rituximab prednisolone therapy) at 12 months = 25% (occurrence of wAIHA)

  Relative Risk Reduction = (CER-EER)/CER = 66%
  Absolute Risk Reduction = (CER-EER) = 49%
  Number Needed to Treat = (1/AAR) = 2

Do they apply to my patient? [explain]

No because the exclusion criteria for the study included previous rituximab treatment, treatment with immunosuppressive or anti-neoplastic drugs within the last 3 months, and hemolytic anemia secondary to autoimmune disease within the last 6 months. The patient was currently being treated with rituximab and received ibrutinib, which is an anti-neoplastic drug, had already been treated with a steroid and the wAIHA was secondary to CLL. However the study applies by default because it is the first and only randomized trial to investigate the treatment of wAIHA with the use of rituximab and prednisone. Furthermore, there are no practice guidelines for the treatment of wAIHA.

Bottom Line:

The results of the RCT demonstrate that using a combination of prednisolone and rituximab as first-line therapy in patients with newly diagnosed wAIHA leads to significantly higher response rates and longer relapsed free survival than can be achieved by prednisolone monotherapy. The combination therapy avoids the serious adverse events of an increased prednisone equivalent dosage because a smaller amount of prednisone equivalent dosage is administered with the rituximab. This would benefit this patient by avoiding the side effects of high dose steroid use. Harms included dyspnea and fatigue which was statistically insignificantly in comparison to the monotherapy/control group.

Outcome for your patient

The patient forwent treatment because she did not have any feelings of fatigue, moreover she was hesitant to take any treatment containing a steroid because of previous side effects she experienced with them. The combination treatment for her wAIHA would be revisited in follow up appointments.

Additional notes/comments/questions:

This patient was not a candidate for splenectomy, which is considered a second line option, because her multiple comorbidities made her a poor surgical candidate, moreover, her diabetes increased her risk of infection which would be compounded if she were asplenic.

A limitation of the study is the small number of the two treatment groups. This is likely due to the small percentage of patients with lymphoproliferative disorders who develop wAIHA. About 5% of these patients develop this condition. A difference of response in a few patients between the two arms of the trial could possibly alter the significance of results of the study, however power analysis of the results in terms of proportions of CR at 12 months was found a power of 0.86, indicating that 86% of equivalent trials will show a significant result.

What was difficult about this critically appraised topic was the dearth of randomized control trial involving treatment of AIHA secondary to lymproliferative disorders. Furthermore, there are no established guidelines for the treatment of AIHA secondary to lymproliferative disorders. Standard treatment has been based upon observational studies.

Overall the study is well designed, and well controlled however the size of the control and experimental groups limits the quality of the evidence, therefore generalizability to routine practice.

The quality of evidence for this treatment is low because there is only one randomized control trial involving it, therefore the strength of recommendation is insufficient.

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Assignment Evaluation

Feedback Date Oct 3, 2016 3:01 PM

Dropbox Feedback

You did well and scored 5, 5, 5, 7, 3. The last section had points off as the patient didnot fit the treatment but you did explain well the issues.

David E Lindsey MD