GROUP NINE

THE EFFECTS OF METHOTREXATE ON PROGRESSION-FREE SURVIVAL AND OVERALL SURVIVAL IN PRIMARY BILIARY CIRRHOSIS

Comment: This is a stellar paper. One of the best I have seen in my years teaching this class. So my comments should be interpreted in that light.

Summary

Background: Primary biliary cirrhosis (PBC) is a potentially fatal chronic liver disease with a presumed autoimmune etiology. Conventional therapy consists of ursodeoxycholic acid (UDCA), which may slow, but does not prevent, disease progression. It has been hypothesized that immunosuppressive therapy may have an impact on disease progression, but previous studies have had small sample sizes.

Objective: We designed a multicenter randomized double blind placebo-controlled trial to examine the effect of methotrexate, an immunosuppressive agent, on survival and progression-free survival in a larger group of patients with PBC.

Methods: We randomly assigned 265 patients with PBC to receive methotrexate plus UDCA (132 patients) or placebo plus UDCA (133 patients). Patients were randomized by histological stage of liver disease. The primary efficacy endpoints were overall survival, defined as time to death, and progression-free survival, defined as time to the earlier of death or development of hepatic encephalopathy, bleeding varices, or ascites. Patients were followed for a median time of 93 months. Kaplan-Meier survival probability estimates were used to compare overall and progression-free survival between treatment groups and Cox proportional hazard regression was used to estimate the risks of death and disease progression associated with methotrexate treatment.

Comment: Excellent to include this. (I cannot come up with your numbers, however. Hopefully you used a KM estimate of the censoring distribution.)

Results: There was no significant difference between the methotrexate and placebo groups in survival or progression-free survival. The risk of death in the methotrexate group was 1.23 compared to the placebo group (95% CI 0.46 to 3.30, p=0.68). The risk of disease progression in the methotrexate group was 1.26 compared to the placebo group (95% CI 0.75 to 2.12, p=0.38). This lack of significance remained when patients were stratified by age and severity of liver disease.

Comment: Not immediately clear to me whether we are concerned about lack of precision in the unadjusted analysis (in which case focus on statistical significance is appropriate) or effect modification (in which case you should comment that the estimated treatment effects remain relatively boring).

Conclusions: Our results do not suggest that methotrexate in addition to UDCA for the treatment of PBC improves progression-free and overall survival compared to patients treated with UDCA alone.

Comment: Of course, those CI are amazingly wide. I probably would have added a bit of a disclaimer in that regard, but perhaps that is best left to discussion.

Background

Primary biliary cirrhosis (PBC) is a chronic progressive cholestatic liver disease. It is primarily a disease of the small intra-hepatic biliary ducts with later damage to the surrounding liver. Death results from liver cirrhosis and its complications, commonly hepatic encephalopathy, bleeding varices and ascites. It is a disease that primarily affects women. An estimated 95% of cases occur in females, with the usual age of onset between 30 and 65 years (*1*). The estimated incidence among U.S. females is 4.5/100,000 person-years (*2*). Median length of survival in symptomatic individuals with PBC ranges from 8 to 15 years (*3*). Survival may be predicted using histological grading on liver biopsy based on the Ludwig classification scale (*4*) or, in the case of transplant free survival, by the Mayo risk score (*5*), which considers several laboratory and clinical variables such as bilirubin, albumin, age, prothrombin time, and edema.

Ursodeoxycholic acid (UDCA) has been the mainstay of treatment for PBC since the late 1980's. Evidence for the benefit of UDCA is especially strong for patients with early stage liver disease, which is defined as Ludwig stage 1 or 2. One study showed that the four-year probability of patients treated with UDCA remaining in early stage disease was 76% compared with 29% in patients treated with placebo (*6*). There is less evidence for the efficacy of UDCA in advanced stage disease (Ludwig stage 3 or 4). If initiated at an early stage, UDCA appears to delay progression of disease, while in advanced stage liver disease UDCA appears to have little to no effect on disease progression (*7*). While two meta-analyses of UDCA in the treatment of PBC did not show any reductions in mortality from PBC (*8*, *9*), treatments for PBC are difficult to assess in trials as the disease process has a slow and variable rate of progression.

PBC is thought to be due to an inappropriate autoimmune response primarily mediated by antigen specific T- and B-lymphocytes. Several auto-antibodies may be detected in patients with PBC. Given this pathologic mechanism, a number of immunosuppressive therapies have been examined for the possible treatment of PBC. Methotrexate (MTX) is a folate antimetabolite that inhibits DNA synthesis. It is commonly used in several autoimmune diseases, including rheumatoid arthritis, sarcoidosis and psoriasis. Two studies on the treatment of PBC with MTX have shown improvement in clinical

parameters including transaminases and bilirubin, although no effect on mortality (10, 11). These studies were small, however, with 10 patients in one study and 86 patients in another. We report the results of a multicenter randomized, double blind placebo-controlled clinical trial to assess the use of MTX for treatment of primary biliary cirrhosis.

Questions of Interest

The primary question of interest is whether MTX treatment leads to improved progression-free survival or overall survival relative to placebo. Additionally, we were interested in whether progression-free survival and overall survival related to treatment differ with respect to age and histological stage. We compared baseline demographic, as well as physiologic measurements predictive of liver disease, to assess the randomization of patients between treatment groups.

Comment: So here you committed yourself to an interest in effect modification. In that case, the Summary should have commented on the estimates more than the statistical significance.

Materials and Methods

Study Design: The study was a multicenter randomized double blind placebo-controlled trial of efficacy of MTX in combination with standard UDCA therapy versus placebo in combination with UDCA therapy in the treatment of moderately advanced PBC. Primary efficacy endpoints were survival, defined as time to death, and progression-free survival, defined as time to the earlier of death or development of hepatic encephalopathy, bleeding varices, or ascites. Patients were recruited from 12 different clinical centers throughout the US. The Institutional Review Board at each center approved the study protocol prior to the subject enrollment period.

Comment: Here you could comment on the planned or actual length of follow-up. But as noted below, that is also a "Result" of the trial. That is, to the extent that follow-up is affect by post-randomization variables, it is a Result. To the extent that it is affected only by the time of randomization of each patient and the time of data analysis, it is a "Material and Method".

Patient Selection & Randomization: Of 535 patients screened, 385 met both inclusion and exclusion criteria and 265 patients were randomized to receive either UDCA plus MTX (maximum dose 20 mg per week) (132 patients) or UDCA plus placebo (133 patients). A total of 10 patients were randomized despite failure to meet all eligibility criteria (9 patients in the MTX group and 1 patient in the placebo group). Randomization was stratified by histological stage of liver disease (stage 1-4) based on the Ludwig method of classification. Two patients in the placebo group were found post-randomization to have failed to meet all eligibility criteria and 2 patients judged to have stage 3 disease were randomized with the stage 1-2 group. Patients continued treatment or placebo throughout the duration of the study unless death, liver transplantation, severe drug toxicity, alcohol abuse, risk of pregnancy, a cancer diagnosis, or voluntary withdrawal occurred. Patients who stopped treatment or declined testing or procedures were still considered for evaluation of the primary efficacy endpoints, including death, hepatic encephalopathy, bleeding varices and ascites.

Comment: But stratification was only at two different levels: Stage 1or 2 vs Stage 3 or 4.

Data Sources: Data on selected demographic characteristics and physiologic measures assessed at the time of randomization were collected from the 265 patients included in this study. Comparison of these baseline variables permitted assessment of the extent of similarity between patients randomized to each treatment group. Basic demographic variables included age, sex, weight, and height. Information on the duration of PBC prior to randomization, as well as clinical measures of liver damage (serum alkaline phosphatase and ALT), liver function (total bilirubin, albumin, prothrombin time, and serum cholesterol), and liver inflammation and cirrhosis (history of splenomegaly, platelet count, and histological stage), were recorded. Data on such physiologic measures during the time of follow-up, however, were not available. For each patient, the primary efficacy endpoints of death, hepatic encephalopathy, bleeding varices, and ascites were assessed at routine patient follow-up, permitting calculation of time to death and time to clinical progression.

Statistical Analysis: Missing measurements were excluded in the descriptive statistics by treatment group, as indicated in the Table 1 footnotes. Summary measures are reported as the mean ± SD or median for continuous variables and percentages for categorical variables. As the primary analyses performed in this study did not require the consideration of variables with missing measurements, all patients with missing measurements were included in the survival analysis. Groups were analyzed by intention-to-treat. The Kaplan-Meier method was used to estimate survival probabilities for groups defined by treatment arm and stratified by age and category of liver disease stage. We chose to stratify subjects on age, as age is a predictor of mortality risk in the Mayo model. The median age of 50 years in study subjects was chosen to define two age groups: age <50 years old and age ≥50 years old. Patients were categorized to early stage liver disease (Ludwig stage 1 and 2 disease) and advanced stage liver disease (Ludwig stage 3 and 4 disease) groups as this stratification approach is commonly used in studies of PBC. Survival was analyzed as overall survival (time to death) and progression-free survival (time to death, hepatic encephalopathy, bleeding varices, or ascites) at 12-month intervals from baseline. Cumulative survival probability estimates and 95 percent confidence intervals are reported. Student's *t*-test was used to compare the estimated difference in survival or progression free survival for groups defined by treatment arm, overall and stratified by age and extent of liver disease. The estimated difference, 95 percent confidence intervals and *p*-values are

Comment: You could either leave these sentences out, or combine them with your later sentence describing the stratified comparisons. As you have it here, the reader is led to believe the primary analysis is the stratified analysis, while in your Question of Interest, the mention of stratification seems to be closer to effect modification.

reported. Cox proportional hazard regression was performed to examine the risk of death or disease progression for groups defined by treatment arm, overall and stratified by age and extent of liver disease. Risk estimates, 95 percent confidence intervals and *p*-values are reported. All reported *p*-values are two-sided and a *p*-value of ≤ 0.05 was considered statistically significant. All statistical analyses were performed using STATA version 9 for Windows (StataCorp LP, College Station, TX, USA).

Comment: the relative risk of death for MTX compared to Placebo (I sometimes even add " a HR less than 1 suggests better survival on MTX")

Results

As expected in a randomized trial, regardless of assigned treatment group (MTX or placebo), patients were demographically similar (Table 1). Patients entered the trial between the ages of 25 and 70 years, with the mean age of those receiving placebo and MTX being 52.2 ± 8.6 years and 50.4 ± 8.7 years, respectively. Approximately 92% of patients in each group were female. Patients weighed between 42.7 and 149.1 kg, with an average weight (±SD) of 73.3 ± 16.2 kg and 70.1 ± 14.4 kg in the placebo and MTX groups. The range of the body mass index (BMI, calculated as weight in kg/height in meters^2) was 17.1 to 53.4, with an average BMI (±SD) of 27.3± 5.41 and 26.1 ± 4.67 in the placebo and MTX groups, respectively.

Across treatment groups, patients were comparable on selected baseline physiologic measures of liver damage, liver function, and liver inflammation and cirrhosis, although the median duration of primary biliary cirrhosis at the time of randomization was slightly longer for those assigned to receive MTX than placebo (983 vs. 867 days). Only seventeen patients presented with abnormal levels of bilirubin (≥2.0 mg/dl), albumin (<3.4 g/dl), and/or prothrombin time (>13.5 sec) based on the Mayo model of independent predictors of prognosis. In terms of histological stage, although a greater proportion of patients in the placebo than MTX group had Stage 1 (18.1% vs. 9.9%) and Stage 4 (16.5% vs. 12.1%) disease, the proportion with early (Stage 1 or 2, placebo: 48.2% vs. MTX: 45.5%) and advanced (Stage 3 or 4, placebo: 51.8% vs. MTX: 54.5%) disease was nearly equivalent between groups, as patients were randomized to treatment using this dichotomous definition of stage.

Comment: Is a four month difference in duration of disease clinically important? (Recall you were quoting 8-15 year timeframe for progression to death) If it is not so important, you need not even comment on it here

Kaplan-Meier estimates of the probabilities of the two outcomes of interest, progression-free survival and overall survival, are presented at 36, 60, and 96 months for each treatment group in Table 2. The probability of overall survival did not decrease as much over time as did the probability of progression-free survival. At each 12-month interval from baseline, probabilities of progression-free and overall survival tended to be similar across treatment groups.

Comment: Here you should report on the length of follow-up for each treatment group. While this is a little bit "Materials and Methods", patient dropout due to adverse events, etc. make this also a "Result". I would also have included a bit on compliance with the drug.

Estimated probabilities of progression-free and overall survival between treatment groups did not differ significantly (Table 3), and the Kaplan-Meier curves for patients receiving MTX and placebo appeared similar with respect to each outcome (Figure 1, Panel A). For example, at 60 months post-randomization, the probabilities of progression-free survival and overall survival were 3.8% lower (95% CI: -12.0% to 4.4%, *p=0.37*) and 0.9% lower (95% CI: -5.8% to 4.0%, *p=0.73*), respectively, in the MTX than placebo group. The estimated risk of clinical progression associated with MTX treatment compared to placebo was 1.26 (95% CI: 0.75 to 2.12, *p=0.38*), and the estimated risk of death associated with MTX treatment compared to placebo was 1.23 (95% CI: 0.46 to 3.30, *p=0.68*). As, none of these results attained statistical significance, the data do not suggest that treatment with MTX is related to better progression-free or overall survival.

Comment: Probably a good idea to give the probabilities for each group along with the difference in those probabilities. Some readers will be comparing the probabilities to what they would have expected for similar patients in order to judge generalizability of results. Also, if probabilities are really low, some readers will be trying to translate into relative risks.

Probabilities of progression-free and overall survival related to treatment did not appear to differ according to either age or histological stage (Table 3). As shown in Panel B of Figure 1, Kaplan-Meier curves were similar between younger patients (patients age less than 50 years) taking MTX versus placebo and between older patients (patients age 50 and greater) taking MTX versus placebo, for both survival outcomes. The estimated risk of clinical progression associated with treatment was 0.84 (95% CI: 0.35 to 1.98, *p=0.69*) for younger patients and 1.67 (95% CI: 0.87 to 3.19, *p=0.12*) for older patients. The estimated risk of death associated with treatment was 1.97 (95% CI: 0.21 to 18.75, *p=0.55*) for younger patients and 1.29 (95% CI: 0.42 to 3.92, *p=0.66*) for older patients. As shown in Panel C of Figure 1, Kaplan-Meier curves were similar between patients with early disease taking MTX versus placebo and between patients with advanced disease taking MTX versus placebo for both outcomes. The estimated risks of clinical progression associated with treatment were 2.11 (95% CI: 0.72 to 6.19, *p=0.17*) for early disease and 0.99 (95% CI: 0.55 to 1.80, *p=0.98*) for advanced disease. The estimated risks of death associated with treatment were 4.31 (95% CI: 0.48 to 38.58, *p=0.19*) for early disease and 0.71 (95% CI: 0.22 to 2.29, *p=0.57*) for advanced disease. Differential effects according to other factors known to predict survival among patients with primary biliary cirrhosis, including total bilirubin, albumin, and prothrombin time, were not examined, given that such measurements for the majority of subjects were in clinically normal ranges.

Comment: And were in the opposite direction of what we had hoped. I would definitely stress that fact.

Comment: Just an aside (I don't have very much to comment on otherwise, I guess): Consider the difference in connotation between "early" and "late" disease versus "less severe" and "more severe" disease. We often use these two classifications interchangeably, but in a disease that we don't understand, we may well learn that the question is more one of severity than duration.

Discussion

In this randomized trial, we sought to test the efficacy of MTX plus usual treatment on survival and progression-free survival among 265 patients with PBC. With a median of 93 months of follow-up, we did not find any statistically significant difference in either primary endpoint across treatment groups.

Comment: Actually, we were more testing effectiveness than efficacy, but that is a fine point.

Comment: Should have been mentioned in Results and/or Materials and Methods, too. Also, are you trying to make a point about whether this was long enough for any important effect to be observed? If so, state that exactly

In evaluating the effect of MTX on our primary endpoints, we felt that it was important to consider subgroups of patients for which MTX might improve overall or progression-free survival. Severity of PBC can be predicted by histological staging, as well as by age, bilirubin, albumin, prothrombin time, and edema. However, we did not examine differential effects with respect to bilirubin, albumin, and prothrombin time, as the vast majority of our patients had levels that were within normal range. Analysis by the traditional grouping of early stage (Ludwig stage 1 or 2) versus advanced stage (Ludwig stage 3 or 4) liver disease showed no difference in survival across treatment groups. There was also no difference in survival associated with treatment among patients age <50 and ≥50 years. Although these analyses were limited in statistical power, these results suggest that MTX does not improve overall survival or progression-free survival, even for certain subgroups of patients.

As aforementioned, the lack of sufficient number of patients exhibiting abnormal physiologic measures related to liver function and disease at baseline could be a limitation of this study, if truly there is a difference in treatment effect by severity of disease. Despite the inclusion of 53% patients with advanced liver disease by histological staging (Ludwig stage 3 and 4 disease), our patients had good hepatic synthetic function based on laboratory values. This constraint could have decreased our ability to detect a difference in the clinical endpoints of survival and progression-free survival associated with treatment, because our patients could have been less likely to progress to our endpoints than histological stage alone would have predicted. Given that PBC is a heterogeneous disease in which patients who do not have evidence of severe hepatic dysfunction can be expected to have median survival rates of 10-15 years and more, our study may have been underpowered to detect our primary end points.

Comment: Excellent point. You could then tie this in to the compliance to decide whether we should have just followed the subjects longer or not. Of course, you do not really have the data in this dataset to be able to do this. But the idea is an important one. I personally viewed the fact that compliance was pretty low by 8 years was motivation for giving up on MTX. But this is a point that needs to be discussed at greater length than this paper would allow.

An exploratory analysis of our data suggests that there may be an overall survival benefit in the MTX patients who had stage 4 liver disease. Plotting survival curves for the four stages separately shows that patients with stage 4 liver disease tended to have much worse overall survival. However, based on 38 patients with stage 4 disease, we are not able to draw inferences about whether treatment is most effective among those with severely advanced disease. Future trials should consider enrolling patients with more advanced disease (as demonstrated by markedly abnormal bilirubin and albumin levels or prothrombin times) as this could demonstrate a difference in risk of death.

Another limitation was the lack of follow-up laboratory data, such as bilirubin or albumin, which may indicate progression of disease in PBC. While observed changes in such values may be less compelling evidence of a treatment effect than end points such as survival, these surrogate end points may show a treatment effect that would otherwise be difficult to demonstrate given the chronic and variable nature of PBC. Finally, although 92% of patients in this study were female, the gender distribution of disease was not considered to be a limitation of this study, as the study population reflects the gender distribution of disease in the general population. Nonetheless, we were limited in our ability to examine the effect of MTX treatment on survival and progression-free survival in men with PBC.

In the largest study to date of the use of MTX plus usual treatment in PBC, we found no statistically significant difference in the primary endpoints of survival or progression-free survival compared to placebo plus usual treatment. Given the variable natural history of PBC, future trials to assess treatment and survival could strive to enroll patients with laboratory and clinical markers of more advanced disease.

Comment: But we did not rule out a halving of the risk of death. Any comments on that?

References

1. Kaplan MM. Primary biliary cirrhosis. N Engl J Med 1996; 335:1570.

2. Kim WR, Lindor KD, Locke III GR, et al. Epidemiology and natural history of primary biliary cirrhosis in a U.S. community. Gastroenterology 2000; 119:1631.

3. Christensen E, Crowe J, Doniach D, et al. Clinical pattern and course of disease in primary biliary cirrhosis based on an analysis of 236 patients. Gastroenterology 1980; 78:236–246.

4. Ludwig J, Dickson ER, McDonald GS. Staging of chronic nonsuppurative destructive cholangitis (syndrome of primary biliary cirrhosis). Virchows Arch A Pathol Pathol Anat 1978; 379:103.

5. Dickson ER, Grambsch PM, Fleming TR, et al. Prognosis in primary biliary cirrhosis: Model for decision-making. Hepatology 1989; 10:1.

6. Poupon R, Chazouilleres O, Balkau B, Poupon RE. Clinical and biochemical expression of the histopathological lesions of primary biliary cirrhosis. UDCA-PBC Group. J Hepatol 1999; 30:408-412.

7. Prince M, Chetwynd A, Newman W, et al. Survival and symptom progression in a geographically based cohort of patients with primary biliary cirrhosis: Follow-up for up to 28 years. Gastroenterology 2002; 123:1044.

8. Goulis J, Leandro D, Burroughs AK. Randomised controlled trials of UCDA therapy for primary biliary cirrhosis: a meta- analysis. Lancet 1999; 354(9184):1053-60.

9. Neuberger J. URSO: panacea or placebo? Hepatology 2000; 31(4):1027-8.

10. Bonis PA, Kaplan M. Methotrexate improves biochemical tests in patients with primary biliary cirrhosis who respond incompletely to ursodiol. Gastroenterology 1999; 117(2):395.

11. Kaplan MM, Schmid C, Provenzale D, et al. Low-dose methotrexate is ineffective in primary biliary cirrhosis: long-term results of a placebo-controlled trial. Gastroenterology 1999; 117(5):1173.

Table 1. Descriptive Statistics of Baseline Patient Characteristics by Treatment Group

	Placebo[1] (n=133)					Methotrexate[2] (n=132)				
	mean	std dev	min	median	max	mean	std dev	min	median	max
Demographic characteristics										
Age at randomization, yrs	52.2	8.6	25.0	53.0	67.0	50.4	8.7	31.0	50.0	70.0
Sex, %										
Male	7.5					7.6				
Female	92.5					92.4				
Weight, kg	73.3	16.2	46.0	70.3	149.1	70.1	14.4	42.7	68.3	114.2
Height, cm	163.7	8.1	149.5	162.7	191.9	163.7	7.9	142.8	162.2	181.6
BMI, kg/m^2	27.3	5.4	17.1	26.8	53.4	26.1	4.7	17.6	25.3	43.2
History of primary biliary cirrhosis										
Duration[3], days	1339.1	1194.7	185.0	867.0	5269.0	1280.3	1262.1	202.0	983.0	6552.0
Indicators of liver damage										
Serum alkaline phosphatase, U/I	244.9	187.4	63.0	200.0	1127.0	242.8	145.7	50.0	208.5	930.0
Serum ALT, U/I	50.2	41.6	9.0	38.0	314.0	54.3	41.4	9.0	42.0	199.0
Indicators of liver function										
Total bilirubin, mg/dl	0.7	0.4	0.1	0.7	2.3	0.7	0.4	0.1	0.6	2.8
Albumin, g/dl	4.0	0.3	3.1	4.0	4.9	4.0	0.4	3.0	4.0	5.9
Prothrombin time, sec	11.4	1.1	8.6	11.5	13.9	11.2	1.1	8.5	11.4	14.6
Serum cholesterol, mg/dl	235.8	58.8	128.0	224.5	560.0	239.2	58.2	137.0	233.0	472.0
Indicators of liver inflammation & cirrhosis										
Splenomegaly, %	10.5					8.4				
Platelet count, 1000 cells/cu mm	234.7	83.2	77.0	235.0	561.0	243.5	88.6	86.0	231.5	619.0
Histological stage of liver disease, %										
Stage 1	18.1					9.9				
Stage 2	30.1					35.6				
Stage 3	35.3					42.4				
Stage 4	16.5					12.1				

[1] For the placebo group: missing data on weight (n=1), height (n=1), serum ALT (n=1), and serum cholesterol (n=2)
[2] For the methotrexate group: missing data on serum ALT (n=1), prothrombin time (n=4), and splenomegaly (n=1)
[3] Time from diagnosis to randomization

Table 2. Probabilities of Progression-Free Survival and Overall Survival by Treatment Group

	Placebo		Methotrexate	
	Estimate	95% CI	Estimate	95% CI
Progression-Free Survival				
36 mo	0.922	0.860, 0.957	0.930	0.871, 0.963
60 mo	0.890	0.821, 0.933	0.852	0.778, 0.903
96 mo	0.788	0.698, 0.854	0.744	0.652, 0.815
Overall Survival				
36 mo	0.983	0.936, 0.996	0.984	0.937, 0.996
60 mo	0.966	0.913, 0.987	0.958	0.901, 0.982
96 mo	0.935	0.866, 0.969	0.908	0.828, 0.952

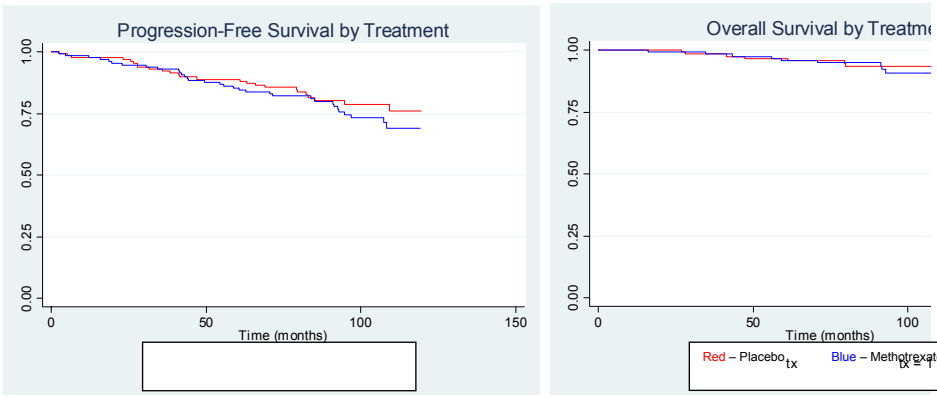
Table 3. Estimated Differences in Survival Probabilities and Risk of Disease Progression and Death Between Treatment Groups -- Overall,

	Methotrexate vs. Placebo										
				By Age Group					B		
	All Patients			Age <50 years			Age 50+ years			Early Stage	
	Estimate	95% CI	*p*	Estimate	95% CI	*p*	Estimate	95% CI	*p*	Estimate	95% CI
Probabilities of Progression-Free Survival											
36 mo	0.009	-0.055, 0.073	*0.79*	0.080	-0.015, 0.176	*0.10*	-0.047	-0.140, 0.046	*0.32*	-0.019	-0.077, 0.0
60 mo	-0.038	-0.120, 0.044	*0.37*	0.038	-0.084, 0.159	*0.54*	-0.100	-0.216, 0.016	*0.09*	-0.056	-0.143, 0.0
96 mo	-0.045	-0.157, 0.068	*0.44*	0.009	-0.163, 0.180	*0.92*	-0.144	-0.299, 0.011	*0.07*	-0.089	-0.214, 0.0
Risk of Disease Progression	1.26	0.75, 2.12	*0.38*	0.84	0.35, 1.98	*0.69*	1.67	0.87, 3.19	*0.12*	2.11	0.72, 6.1
Probabilities of Overall Survival											
36 mo	0.0002	-0.032, 0.032	*0.99*	-0.016	-0.048, 0.016	*0.31*	0.008	-0.038, 0.055	*0.73*	-0.035	-0.084, 0.0
60 mo	-0.009	-0.058, 0.040	*0.73*	-0.051	-0.107, 0.005	*0.08*	0.017	-0.049, 0.082	*0.62*	-0.054	-0.113, 0.0
96 mo	-0.026	-0.102, 0.049	*0.50*	-0.019	-0.102, 0.065	*0.66*	-0.055	-0.176, 0.067	*0.38*	-0.060	-0.149, 0.0
Risk of Death	1.23	0.46, 3.30	*0.68*	1.97	0.21, 18.75	*0.55*	1.29	0.42, 3.92	*0.66*	4.31	0.48, 38.5

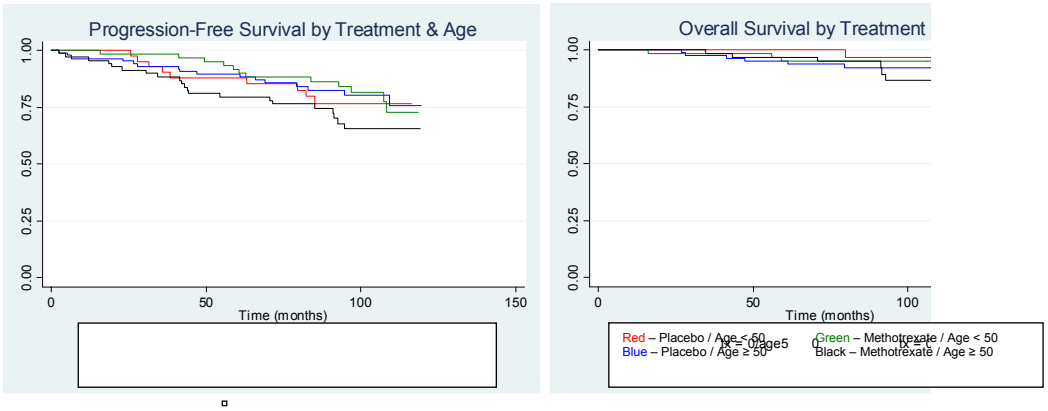
Comment: Probably a good ide to make clear these HR are MTX:placebo.

Figure 1. Kaplan-Meier Estimates of Progression-Free and Overall Survival by Treatment, by Treatment & Age, and by Treat

PANEL A

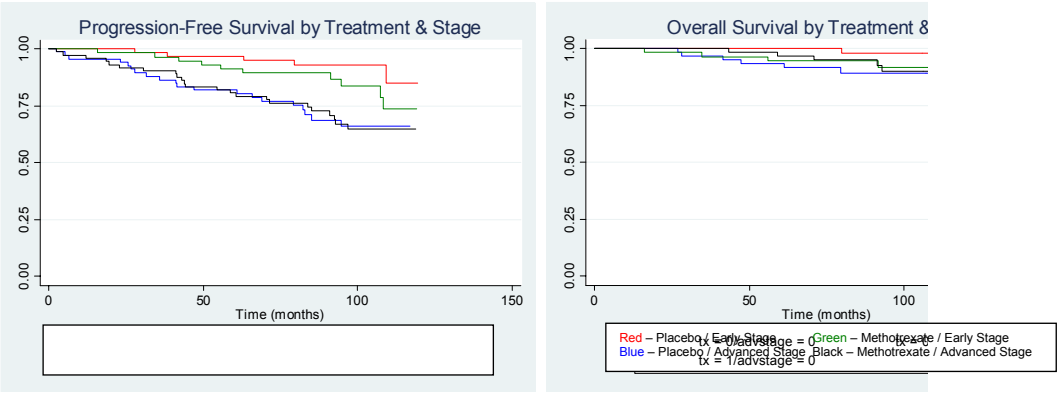


PANEL B



Comment: It's always about me: I can only see three colors on these graphs: Black, blue, and a color that is neither black nor blue. Hardly a big deal, as it turns out. I just felt a need to add a comment here.

PANEL C


Progression-Free Survival by Treatment & Stage
1.00
0.75
0.50
0.25
0.00
0
50
100
150
Time (months)
Overall Survival by Treatment &
1.00
0.75
0.50
0.25
0.00
0
50
100
Time (months)
Red – Placebo / Early Stage
Green – Methotrexate / Early Stage
Blue – Placebo / Advanced Stage
Black – Methotrexate / Advanced Stage
tx = 0/advstage = 0
tx = 1/advstage = 0