The crux of the log rank test. Re: Locasciulli A, Oneto R, Bacigalupo A, Socié G, Korthof E, Bekassy A, Schrezenmeier H, Passweg J, Führer M. Outcome of patients with acquired aplastic anemia given first line bone marrow transplantation or immunosuppressive treatment in the last decade: a report from the European Group for Blood and Marrow Transplantation. Haematologica 2007; 92:11-8

Haematologica 2007; 92:e122 DOI: 10.3324/haematol.11941

Dear Sirs,

with interest we have reviewed the recent paper of Locasciulli *et al.*[1] in your *Journal.* The authors analysed overall survival rates (OS) of an impressingly high number of patients (n=2479) with acquired aplastic anaemia (AA) with respect to primary treatment, bone marrow transplantation (BMT) versus immunosuppressive therapy (IST). Kaplan Meier curves in combination with log rank test were used for the analysis of survival. The authors found a highly significant difference (p=0.002) between the survival curves of patients with BMT and IST (Figure 1), from which they suggested that *10 year survival was significantly better in patients treated with BMT than in those in whom IST was used (73% versus 68%, respectively)*. In our understanding, the graphs have to be interpreted differently: While the difference between the two survival curves is statistically highly significant, we find that IST is superior to BMT. Whereas the survival curve of BMT shows a steep decline during the first 15 months of treatment, possibly related to transplantation related mortality, the IST curve has a steadier downward slope, reaching the level of BMT after 60 months. Thus, superiority of IST over BMT seems evident.

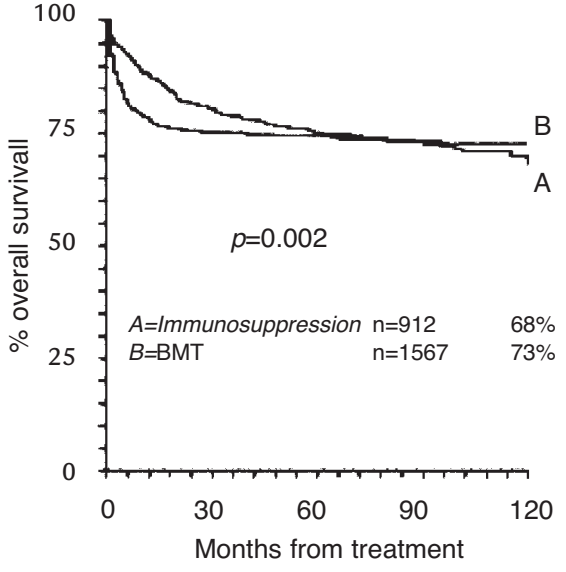

Figure 1. from Locasciulli *et al.*, Haematologica 2007. A) immunosuppressive therapy (IST), B) bone marrow transplantation. While curve A decreases slowly over time, curve B shows a steep decline. Therefore, this Kaplan Meier plot should be interpreted in favour of IST. p=0.002 (derived from a log rank test) denotes statistical significance.

It is a common misunderstanding of the log rank test to postulate a significant p value would indicate a difference between the two curves at a specific arbitrary time point (f. e. 10 year survival). On the contrary, the log rank test compares two survival curves taking into account the whole follow-up period. This becomes obvious when looking at the log rank statistic LR. LR is the sum of $(O_i - E_i)^2/E_i$ over both groups i=1,2, where O_i and E_i are the totals of the observed and expected events in group i.[2] Under H_0, LR follows a χ^2 distribution with 2 degrees of freedom, so the p-value can be determined from respective tables. In a second step the plotted graphs have to be interpreted. The log rank test is not to be used, when two survival curves show a crossing over in their course.[3] Furthermore, the median follow-up in the study of Locasciulli *et al.* was 41 months and 54.5 months in the BMT and IST group, respectively. Thus, it does not seem recommendable to compare 10 year survival times without showing the confidence intervals around the Kaplan Meier graphs. Putting the rule to the test would be to compare survival at 10, 20 or 30 months, when the results are unambiguous.

Locasciulli *et al.* have not laid further emphasis on this primary finding in the discussion section. Hence, the principle statements of this paper remain unchanged.

Yours sincerely.

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References

1. Locasciulli A, Oneto R, Bacigaloupo A, Socié G, Korthof E, Bekassy A, et al. Outcome of patients with acquired aplastic anemia given first line bone marrow transplantation or immunosuppressive treatment in the last decade: a report from the European Group for Blood and Marrow Transplantation. Haematologica 2007; 92:11-8.
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