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POOLED ANALYSIS OF TWO PROTOCOLS OF INTERMITTENT HORMONAL THERAPY, IN ADVANCED PROSTATE CANCER

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BACKGROUND/OBJECTIVES

Few randomized studies have compared intermittent hormonal therapy with continuous therapy for the treatment of advanced prostate cancer. We present pooled results from two randomized trials, with similar protocols and identical data collection. The objective is to compare overall and cause specific survival in patients receiving therapy compared to those receiving continuous therapy.

MATERIALS & METHODS

In MAB 626 patients (aged 50-88, mean = 73), were randomized 314 to continuous therapy and 312 to intermittent. In CAB 917 patients (aged 44-81, mean 72) have been randomized - 462 to intermittent therapy and 455 to continuous. The statistical analysis is through a pooled individual level meta analysis with interaction tests to assess the constancy of treatment comparisons across studies. Cox proportional hazards models are used to investigate the effect of treatment (intermittent therapy compared to continuous) on time from randomisation until death. In a prognostic factor analysis the effects of age, T Category, Metastatic Status, Gleason Score and PSA at randomisation are investigated. Interaction tests are used to assess if the effects of these prognostic factors are the same in the two studies.

MAB Patients received cyproterone acetate (CPA) 200 mg for two weeks and then monthly depot injections of a LHRH analogue plus 200 mg of CPA daily during induction. Patients randomised to the intermittent arm ceased treatment while those randomised to the continuous arm received 200 mg of CPA daily plus a LHRH analogue. CAB patients received CPA 200 mg for two weeks and then monthly depot injections of a LHRH analogue plus 200 mg of CPA daily during induction. Patients randomized, to the intermittent, received when on treatment 300 mg CPA and the continuous arm the same induction treatment.

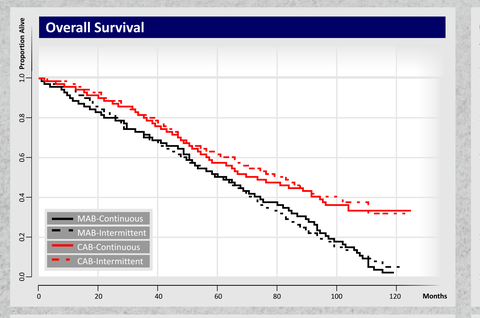
RESULTS

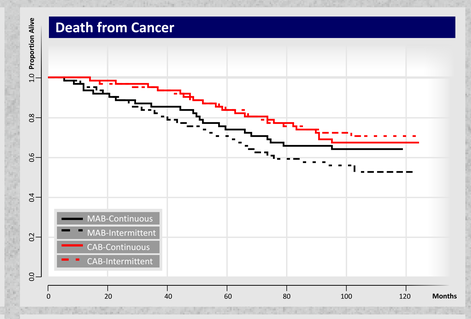
The median time on study for patients in the Mab trial was 57 months and for the Cab study is 54 months. There are a total 4213 person years at risk on Cab and 2887 on Mab; these are equally split between the two treatment arms, 3514 years for Continuous therapy and 3586 for Intermittent.

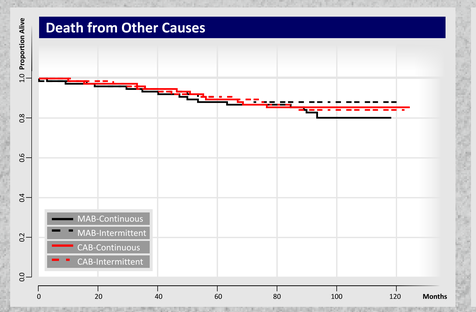
There are differences between the two studies in terms of the patients recruited. In Mab there are more older patients, more T4, more M1, more G3, more Gleason 8+, and more with higher PSA at randomization.

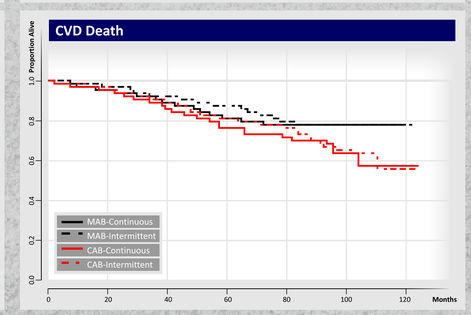
PSA at randomization was a design issue and to be randomized on CAB PSA had to be less than 4 ng/ml.

A total of 474 patients are known to have died in the MAB study and 421 in the CAB study.









OVERALL SURVIVAL

There was no evidence that the effect of intermittent therapy of overall survival was different in the two studies, p = 0.25 and pooling the data is appropriate.
Survival in the Cab study is better than in the Mab, P<0.0001 with a hazard ratio of 0.64 (95% CI 0.56, 0.72). This can probably be explained by a better selection of patients for inclusion in CAB – lower psa and less metastatic.
There is no difference in overall survival, adjusting for study as the death rate in CAB is lower than in MAB, p = 0.0.77, with hazard ratio (HR) 0.98 (95% CI 0.86 to 1.12).

CAUSE SPECIFIC SURVIVAL

In MAB 51% of deaths were due to cancer and 28% due to CVD, with 21% other causes, while in CAB 36% of deaths were cancer deaths and 46% CVD and 19% other causes.
In both studies there are fewer CVD deaths in the intermittent arm HR = 0.87 (95% CI 0.70, 1.09), p= 0.22.
While in MAB, in particular, there are more cancer deaths in the intermittent arm HR = 1.29 (95% CI 0.99, 1.65), p=0.054 but not in CAB, HR = 0.98 (95% CI 0.71, 1.34), p=0.90.
Overall the hazard of death from other causes is lower in the intermittent arm (HR = 0.83, (95% CI 0.62, 1.12), p = 0.23
There is no statistical evidence of differential effects in the two studies with regard to CVD (p=0.58) and cancer deaths (p=0.16) and other causes (p=0.33).

PROGNOSTIC FACTOR

Metastatic status, high Gleason Score, older age and higher PSA are all associated with poorer survival.
There is no evidence that the effects of the prognostic factors varied over the two studies, p = 0.53
Adjusting for these the HR of death from any cause in CAB is HR= 0.81, 95% CI (0.70, 0.94) p < 0.01. This is still significant so these prognostic factors do not explain all the differences in survival between MAB and CAB.
Adjusting for the prognostic factors there is still no evidence of any difference between Intermittent and Continuous therapy with a hazard ratio of HR=0.99, p5% CI 0.87, 1.14), p = 0.99.

CONCLUSIONS

Intermittent therapy should be considered for use in routine practice since it is associated with no reduction in survival, no clinically meaningfull imparment in quality of life, better sexual activity and considerable economic benefit to individual and community.

S.E.U.G.