PHASE 3 STUDY OF INTERMITTENT MONOTHERAPY VERSUS CONTINUOUS COMBINED ANDROGEN DEPRIVATION

INTRODUCTION AND OBJECTIVE

Intermittent androgen deprivation therapy can only be appropriately evaluated in a randomized fashion. We present updated follow up results, to Sept 2017, from the SEUG 9901 Phase III study comparing the intermittent monotherapy with continuous combined androgen deprivation using an LHRR analogue and ciproterone acetate and associated components of quality of life. The study was powered to establish equivalence of mortality in intermittent therapy compared to continuous. Assuming a HR = 1.21 for Intermittent compared to continuous, then based on a one-sided logrank test for equivalence at error rates alpha = 0.05 and beta = 0.20, a total of 658 patients have died; 208 from prostate cancer (106 Intermittent and 102 Continuous), 275 from CVD (131 Intermittent and 144 Continuous), and whose PSA decreases to < 4 ng/ml (preferably <1 ng/ml) after 3 months of induction therapy. Intermittent therapy is less likely to be beneficial for patients with metastasis and bone hot spots, with high initial PSA levels (>100 ng/ml), severe pain or extensive disease. The main reason that the latter group do not benefit from intermittent therapy is that they tend to go on to continuous therapy relatively quickly.

RESULTS

1045 men with a median PSA of 15.9ng/ml were registered between October 1999 and September 2007. 24.5% of registered patients have a PSA less than 10ng/ml; 39.5% of registered patients have a PSA greater than 20ng/ml. 90.3% have a T3 tumour and 5.6% T4; only 14% have metastatic prostate cancer, 63% have Gleason Score 6‐7 and 21% Gleason 8+. 918 patients aged under 60. Men whose PSA falls to between 2 and 4 have an increased hazard of dying relative to those whose PSA falls below 0.5 (HR=1.86, 95% CI 1.52, 2.27). Adjusting for Age, PSA and metastatic status, patients on intermittent therapy had a reduced hazard of death compared to continuous therapy, HR= 0.92 (95% CI 0.79, 1.06), p = 0.27, Figure 1. The hazard of a CVD death is HR=0.84 (95% CI 0.66, 1.06, p = 0.15), Figure 2, while for other metastatic disease it is HR = 1.56 (95% CI 0.86, 2.86, p = 0.14), Figure 3. For Prostate cancer HR = 0.96 (95% CI 0.73, 1.27, p = 0.77), Figure 4, and for other causes of death it is HR = 0.89 (95% CI 0.63, 1.27, p = 0.52), Figure 5.

CONCLUSIONS

Follow up has been extended to a maximum of 17 years and 13% of patients are still in active follow up. We are at the 658 deaths specified in the protocol and there is no evidence that an initial treatment with intermittent therapy is harmful to patients in that overall survival is poorer and we can conclude that intermittent therapy is equivalent to continuous in terms of overall survival. There are no differences in cause specific hazards of death though there is a slight tendency to have slightly poorer survival on continuous therapy driven largely by elevated cardiac vascular deaths over the whole follow up period but particularly up to 10 years following randomization. There is no difference in prostate cancer deaths, though those randomized to intermittent therapy have a higher hazard of a death due to a non-prostate cancer.

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