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Danish Head and Neck Cancer Group

Interim Analysis of DAHANCA 10

Study of the importance of Novel Erythropoiesis Stimulating Protein (Aranesp®) for the effect of radiotherapy in patients with primary squamous cell carcinoma of the head and neck.

The background
The DAHANCA 10 trial was temporarily stopped on October 18 due to information about potential unexpected negative effects related to immunohistochemical estimation of the so-called EPO receptor. As this happened almost simultaneously with the planned interim analysis it was decided to temporarily stop intake of protocol and await the outcome of the analysis before any further decision was taken.

This analysis has now been performed and discussed at the recent DAHANCA meeting on November 28, 2006.

The interim analysis
Prior to the analysis a patient chart review was performed in order to update the data, and in addition the data was run against the central person register in order to get complete survival information as per date (24 November). This latter analysis revealed approximately 20 new deaths in patients with no known failures and the cause of these deaths needs to be explored, but they are in the current analysis considered to be non-cancer related. There is an equal distribution among such deaths in the two groups.

In total 522 patients have been randomized (of a planned intake of 600). Of these six were found to be non-eligible (two had simultaneous oesophagus cancer, two had too high haemoglobin, two withdrew consent after randomization but before completion of treatment). Of the remaining 516 32 were included after July 2006 and are therefore just about to complete treatment or in short follow-up. These patients were included from analysis due to lack of a sufficient follow-up time. The remaining 484 patients are included in the interim analysis.

The following description of the analysis will not in detail describe the events because there is still some additional modification to be done and we will therefore only preserve the overall conclusion and major observations.

The interim analysis has been performed based on intention to treat irrespective of whether the patients have completed the planned radiotherapy and drug treatment according to protocol.

The outcome
Among the 484 patients 158 have experienced a locoregional failure (the primary study endpoint). The planned interim analysis was supposed to after 150 failures, and the additional

8 have been found during the more detailed update we have performed. There have been 196 deaths of which 140 are known to be of the cancer in question.

Overall, **the patients have been evenly distributed according to the stratification parameters** which also were found to be important and were all separating the material significantly except from the parameter of larynx and pharynx site which yield almost the same outcome (the stratification parameters were gender, T and N classification, and tumour site). In addition the patients were stratified according to institution, and there was no difference in outcome as a function of this parameter.

The **compliance to Aranesp has been good** and by far most of patients have achieved the planned and expected increase in haemoglobin (this has not been part of the interim analysis, but this information was generated in connection with the London meeting, January 2006).

The treatment with Aranesp **has not caused ecxess major serious adverse events** and has been well tolerated by the patients included. Thus, there is no knowledge of excess side effects and there is no difference in the probability of dying without cancer as a function of randomization group.

Regarding **the primary endpoint of locoregional failure** there is a small but significant poor outcome in the patients treated with Aranesp. The 3-year actuarial value is in the order of a difference of 10% and with a p value of $p = 0.01$ which is also maintained in a multivariate analysis taking the stratification parameters into consideration.

When evaluating the endpoint of **rall failure** including failure in the T, N, and distant metastasis site there was a similar difference in the order of approximately 10% in disfavour of Aranesp and with a p value of 0.01.

A separate analysis of the distant failure in patients with **distant metastasis alone** showed exactly the same pattern in the two randomization groups indicating no excess in distant metastasis rate in patients without a prior locoregional failure.

The **overall survival** showed a smaller non-significant difference in disfavour of Aranesp ($p = 0.08$). A similar difference was found for the endpoint **of disease-specific death** whereas there was no difference at all in the death rate of patients **dying from other causes** not related to the cancer in question.

All univariate analyses were confirmed to be of the same magnitude in a multivariate setting.

The conclusion

Based on these outcome **results the DAHANCA group concluded that the likelihood of a reverse outcome, i.e. that Aranesp would be significantly better than in control was almost non-existing** even if we await a longer follow-up and additional inclusion of the remaining planned 78 patients. It was therefore decided that the trial should be terminated and futher inclusion stopped. This information will be communicated to the Ethical Committee, the Danish Drug Agency “Lægemiddelstyrelsen”, to the involved departments and to Amgen. In addition, the present report will be communicated to a task force which is evaluating the role of the use of erythropoietin in Denmark. They are planning an update of the recommendations and have been awaiting our preliminary results.

No further reports or detailed information will be disclosed until further analysis and evaluation of the still missing data have been collected.

The future
Based on the above mentioned conclusions we are planning the following:

Continue follow-up and update of information of the patients included in the trial. This includes exploration of cause of death in patients with this parameter being unknown and to collect the still remaining and missing data from a few patients. Furthermore, the follow-up will be continued and planned. The GCP study visits and evaluation will continue until all necessary information has been achieved.

The planned **collection of biological material**, including the collection of the paraffin blocks has been initiated and the **immunohistochemistry analysis of the "EPO receptor"** should be performed similar to what has been done in the German study. We are well aware of the problems related to the specificity of this analysis, but still feel that we should perform it similar to the German study irrespective of what it in fact may measure. In addition, we plan to explore more detailed into the possibilities **of making a more exact estimate of the true receptor** based on RNA expression from RNA fragments to be extracted from the paraffin blocks. We have access to a rather successful technique in that respect. With that purpose the blocks will be collected at the Clinical Trials Centre in Aarhus which will organize the further analysis.

Additional analysis of the compliance and response to Aranesp will also be performed as a part of an already planned Ph.D. study which is expected to start in April 2007. There is abundant material collected in association with the current study and we must expect that this analysis is going to take some time before the data are available.

The structure of the DAHANCA 10 study was in fact more elaborate than just the randomized trials because we also formed and registered patients with high haemoglobin. The analysis of this overall material will therefore also be an integrated part of the final evaluation of the study, especially in order to see whether this cohort of patients here in fact do have a poorer outcome than similar patients with a higher haemoglobin.

The DAHANCA group has done a substantial work in trying to perform this trial which by far is the largest dealing with this specific question. Obviously, we are disappointed with the apparent outcome, but this is indeed the reason why we are doing such clinical trials. We are a bit puzzled by the cause of the specific negative outcome and will on a scientific basis explore that as detailed as possible.

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The DAHANCA 10 protocol