Letter to the editor
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Robert SCHÄFER

# Do high Hb-levels improve therapy outcome of cancer patients? Of tumor hypoxia, anemia and cancer treatment

FLEISHMAN-HILLARD GERMANY GmbH, INTERNATIONAL COMMUNICATIONS, FRANKFURT AM MAIN, GERMANY

Hamburg, October 13, 2000 - (fh-hs) - The influence of oxygen on cancer treatment has gained increased attention during the last decade. It has been known for several years that tumors contain areas hardly supplied with oxygen. These hypoxic regions are more resistant against therapy and possess an increased genomic instability thus leading to enhanced tumor progression and metastases. A possible way of improving tumor hypoxia is to increase the Hb-levels of cancer patients, which may result in a better prognosis. At the Ortho Biotech / Janssen-Cilag media briefing "New aspects for the use of erythropoietin in oncology", held on the occasion of the ESMO congress in Hamburg, an up-to-date review of results and a look into the future were provided by Prof. Dr Juergen Dunst, Halle, Germany, and Prof. Dr Matti Aapro, Genolier, Switzerland.

"Tumor hypoxia is an important factor in cancer therapy," stated Prof. Dunst at the beginning of his presentation. Nearly every solid tumor contains hypoxic areas, regardless of its size, staging or histology. As oxygen is a radiosensitizer, these hypoxic cells are by far more difficult to kill than cells with a normal oxygenation status. "You have to irradiate these cells with about 3-fold the dose necessary for normal cells", explained Dunst. "The same is the case for the efficacy of cytostatic drugs, which preferably destroy fast proliferating cells while hypoxic cells only grow slowly."

Experimental data also show that cells lacking the ability for apoptosis have a growth advantage in hypoxic regions, which might explain the enhanced tumor progression associated with these areas. Hypoxia is also a strong inducer of tumor angiogenesis. As Dunst has shown in clinical trials with patients suffering from cervical cancer, hypoxia stimulates the release of VEGF (Vascular Endothelial Growth Factor), a protein growth factor essential for the development of new blood vessels.

An important factor influencing the severeness of tumor hypoxia is tumor- or therapy-induced anemia, as was shown by several investigators. "While normal tissue can compensate the low $O^2$ partial pressure caused by a low hemoglobin level, tumor tissue cannot. Anemia therefore significantly increases tumor hypoxia. For some types of tumors like cervical cancer or head and neck tumors, it has already been shown that a low Hb-level is an independent negative prognostic risk factor", Dunst explained.

In his opinion it is therefore advisable to treat the anemia of cancer patients to improve their quality of life and most likely their prognosis. This can either be achieved with the donation of blood transfusions or by using the recombinant growth factor erythropoietin. However, blood transfusions possess some unfavorable side effects such as the transmission of infectious diseases, immune suppression and allergic reactions. They also do not allow to keep the Hb-level in a constant range during radio- and/or chemotherapy to improve their quality of life and probably as well their prognosis. "The efficacy of erythropoietin in increasing and maintaining Hb-levels has already been shown in a number of studies with patients suffering from different types of cancer. There is also growing evidence that patients with higher Hb-levels have a better prognosis, speaking in terms of local tumor recurrence and overall survival", resumed Dunst.

In his presentation, Prof. Matti Aapro introduced a recent European multicenter trial examining the influence of erythropoietin treatment during chemotherapy on the need for transfusions, quality of life and overall survival. The EPO-INT-10 trial (Littlewood et al., 2000) comprised 375 patients with solid or hematologic malignancies which were randomized (2:1) to be either treated with Epoetin alfa (Eprex®/ Erypo®) or placebo. Inclusion criteria for patients were treatment with a non-platinum chemotherapy for solid tumors or a hematologic nonmyeloid malignancy, an initial Hb level of <10.5 g/dL or >10.5 g/dL with a decrease of >1.5 g/dL per month or cycle, and a life expectancy of more than 6 months.

"It could be shown that patients in the epoetin alfa group needed significantly less blood transfusions and had higher mean hemo-globin levels than patients treated with placebo," Aapro said. "Furthermore, the overall quality of life in the epoetin alfa group, as assessed by different questionnaires, was also significantly improved compared to the placebo group. Epoetin alfa was well tolerated with similar types and incidences of adverse events."

Until recently Eprex®/Erypo® was approved for the treatment of anemia in patients undergoing platinum-based chemotherapy. Based on the data of the EPO-INT-10 trial, it now also received the approval for the use with non-platinum chemotherapy treatments for solid tumors, malignant lymphomas and multiple myeloma.

"There is a growing number of trials confirming that the treatment of anemia in cancer patients might improve therapy efficacy. Therefore we additionally decided to evaluate the survival data shortly before unblinding the study, though it wasn't originally designed for this purpose", Aapro said. "Surprisingly it could be shown that the median survival in the epoetin alfa group was 17 months, compared to 11 months for patients receiving placebo". The reasons for this are not yet clear and can be various: One factor could be the improvement of tumor oxygenation leading to a better therapy outcome. Another factor might be that patients treated with epoetin alfa, due to their better physical and psycho-logical state of health, had a better therapy compliance. To clarify the reasons for the prolonged survival further studies are currently underway.

## REFERENCES

**1.** Littlewood TJ, Rapoport B, Bajetta E et al. Possible relationship of hemoglobin levels with survival in anemic cancer patients receiving chemotherapy. Proc ASCO 2000; 19: 605a.

## SOURCE

"New aspects for the use of erythropoietin in oncology"
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*Address correspondence to:*
*Mr Robert Schäfer, Fleishman-Hillard Germany GmbH, International Communications, Hanauer Landstraße 182c, D - 60314 Frankfurt am Main, Germany*

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