Perspective

Erythropoietin and cancer - a poorly understood liaison!

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Human recombinant erythropoietin (rhEpo) has been used for many years to treat chemotherapy and cancer associated anemia. The application of rhEpo resulted in an improved quality of life of patients and in a sparing of blood transfusions (1). Studies trying to achieve higher hemoglobin target levels in breast cancer patients then indicated that patients receiving rhEpo had a reduced survival (2). Such observations were confirmed by other studies and a meta-analysis summarizing the data of almost 14,000 patients with cancer from trials 53 trials. Therein the use of erythropoiesis stimulating agents (ESA) increased mortality during the study period [combined hazard ratio (cHR) 1.17,] and worsened overall survival (1.06, 1.00-1.12). The same also applied to patients (10,441 from 38 trials) receiving ESA during chemotherapy also presenting with a slight but significant increase of the mortality rate in the active study period with a cHR of 1.10 (0.98-1.24), and a cHR 1.04 (0.97-1.11) for overall survival (3). Thus, potential benefits in association with improvement of anemia and quality of life have to be counted against a potential reduction of life span.

Importantly, the mechanisms by which ESA treatment can increase mortality in cancer patients remain largely elusive. While effects of ESA on blood viscosity and an associated increased risk for thrombo-embolic complications have been discussed to underlie the increased mortality in cancer patients receiving ESA several alternative mechanisms may be relevance (3,4). First, Epo is a cytokine which activates signal transduction cascades involving the JAK/STAT pathway (5). In addition, Epo not only acts upon binding to the homodimeric Epo receptor (EPOR) in erythroid tissues thereby stimulating erythropoiesis but also targets a heterodimeric receptor formed by one EPOR chain and a beta-common receptor chain which is expressed on extraerythrocytic tissues such as epithelial cells or macrophages (6). By targeting this later receptor on macrophages Epo exerts anti-inflammatory effects by inhibiting NF-κB inducible immune effector pathways (7). This leads to inhibition of pro-inflammatory cytokine expression which has been shown to exert detrimental effects towards host responses against invading microbes (7). Accordingly, by this pathway rhEpo may also weaken anti-cancer immune responses thereby leading to exacerbation of tumor proliferation. This is in a line with the observation that Epo mediated modulation of JAK-STAT signaling cascades was associated with tumor cell invasion in a model of head and neck cancer (8). These data are also linked to the observation that certain cancer cells express receptors for Epo (EPOR), however, the biological functionality of such receptors has been heavily discussed (4). Nonetheless, EPOR have been found in biopsies of patients with breast cancer and were highly expressed in other malignant tissues (9). These and subsequent data also suggested that quantity of EpoR expression was associated with tumor hypoxia (9). In a line with these observations, an increased expression of EpoR in breast cancer patients was associated with a higher risk of local recurrence of cancer in the absence of ESA treatment (10). Further EpoR mRNA expression was positively associated with a positive receptor status for oestrogen and progesteron receptors (10). These data point to the notion that the expression of EPOR is associated with a specific biology of breast cancer cells which per se may be associated with an unfavorable prognosis. This hypothesis is confirmed by recent data indicating that EPOR expression may be involved in tumor progression in HER-2 positive breast cancer cells and that the functionality of EPOR on

cancer cells is linked to resistance against trastuzumab while down-regulation of EPOR on cancer cells could reverse this resistance (11). On the other hand breast cancer tissues with higher EPOR expression responded significantly better to tamxoifen treatment than cancer tissue with low EPOR levels suggesting that EPOR expression may determine the behavior and proliferation kinetics of breast cancer cells per se and the response to different treatment regimen which may be further modified by the concomitant expression of hormone receptors or HER-2 (12).

However, at least in animal models Epo may increase the proliferation of cancer cells and tumor growth by alternative mechanisms. This can first relate to the fact that Epo is able to stimulate angiogenesis by increasing the mobilization and differentiation of endothelial progenitor cells which appears to be a promising approach for the treatment of patients with stroke or cardiovascular disease (4,6). However, such an Epo-inducible effect appears to be unfavorable in association with cancer which has been demonstrated in animal models showing that Epo treatment accelerated growth of EPOR negative cancer cells in mice by stimulating angiogenesis and tumor vascularisation (13). Moreover, Epo affects cellular iron homeostasis (14) and rhEpo treatment of patients can mobilize iron which is needed for heme synthesis during erythropoiesis (1). This is likewise of importance in patients with cancer because rapid proliferating tissues have an essential need for iron which is an essential compound of many metabolic process and enzymes in DNA synthesis (15). Accordingly, an increased availability of iron may promote tumor cell growth by enhancing the supply of this essential nutrient to tumor cells (16) but also by negative effects of iron towards the efficacy of cell mediated immune pathways which play central roles in anti-cancer immunity (17). This ominous association has been recently ascertained by the finding of Torti and co-workers, who demonstrated that the iron status of cancer cells, as reflected by the expression of specific iron metabolism genes, is directly associated with the biological behavior of cancer cells. Specifically, they found that a reduced expression of the iron export protein ferroportin which prevents iron egress from cancer cells was associated with a more aggressive biological behavior of tumor cells and a poor prognosis of patients with breast cancer (18). This also demonstrates that the restriction of iron which underlies tumor associated anemia -also termed as anemia of chronic disease- appears to results from a specific strategy to withhold the essential nutrient and growth factor iron from pathogens in order to better combat infections and cancer (16,17).

In a recent paper Trost and colleagues (19) added a novel facet to the puzzling and ambivalent roles of Epo in cancer biology. They used two breast carcinoma cell lines, MCF-7 and MDA-MB-231, and studied the effects of short term (24 h) and long term (nine weeks) exposure to rhEpo in respect to the tumor cells' growth characteristics and responsiveness to cisplatin induced toxicity. While the stimulation of cells with rhEpo for 24 hours negatively affected their proliferation rate and in parallel their susceptibility to cisplatin mediated toxicity, the long term exposure to rhEpo induced the proliferation kinetics and the vulnerability to cisplatin of MCF-7 but not of MDA-MB231 cells. The underlying mechanisms being responsible for these differences were then further investigated employing chip analysis of both cells after short and long term exposure to cisplatin. These two cell lines differ in respect to their hormone receptor status. While estrogen and progesterone receptors are expressed on MCF-7 cells, only estrogen receptors are found on MDA-MB231 cells. In addition, MCF-7 express a wild type p53 whereas p53 is mutated in MDA-MB231 cells. Further analyses demonstrated that the expression of the apoptosis gene BAD was upregulated in unresponsive MDA-MB-231 cells but decreased in MCF-7 cells after prolonged rhEpo exposure. Accordingly, following the combined exposure to cisplatin and rhEpo several apoptotic genes were differently expressed between the two cells lines also suggesting that rhEpo affects p53 triggered cell responses after exposure to cisplatin.

In summary, these data provided interesting evidence that in responsive cells rhEpo produces contrasting effects in respect to promotion of cell growth and susceptibility to chemotherapy. It will thus be of interest to see in subsequent studies whether or not rhEpo can improve the therapeutic efficacy of certain chemotherapeutic drugs in Epo responsive tumor cells. On the other hand, this study has also shown that the cancer cell responsiveness to rhEpo is determined by specific co-factors such as progesterone receptor positivity or the presence of a functional p53 pathway. This is in accordance with data discussed above on the decisive role of specific receptor expression pattern in breast cancer tissues for the clinical course of the disease or the response to therapy (10-12). However, based on these results it will be of interest to retrospectively analyze the molecular biology of breast cancer tissues in respect to EPO and hormone receptor expression, presence of p53 mutations or HER-2 status, derived from the trials using rhEpo to treat anemia in breast cancer patients (3). A linkage analysis of different cancer cell types with the

outcomes after rhEpo therapy could provide clinically valuable information towards risk/benefit assessment of individual patients in respect to treatment with ESAs.

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