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
tamoxifen 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 progestosterone
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 cell 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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References
