Preclinical and Clinical Studies on The Use of ESAs in Oncology

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Does EPO Stimulate tumor growth?

Does treatment with rhEPO have an effect on survival?

In vitro cellular models

EPO expression and tumor growth: In vitro cellular models

Positive association

Westenfelder et al. 2000
Acs et al. 2001
Acs et al 2003
Acs et al 2004
Batra et al 2003
Mohyeldin et al. 2005
Uchida et al 2004
Belenkov et al. 2004
Kumar et al. 2005
McBroom et al. 2005
Hardee et al. 2006
Solar et al. 2008

Negative association

Berdel et al. 1991
Westphal et al. 2002
Tullai et al. 2004
Kokhaei et al. 2007
Liu et al. 2004
Carvalho et al. 2005
Gerwitz et al. 2006
Hardee et al. 2006
LaMontagne et al. 2006
Hardee et al. 2007
Palumbo et al. 2007

Many of these studies have important limitations

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The results of in vitro studies are highly questionable because of :

- lacking specificity of EPO-R antibodies used, all also detect non-EPO-R proteins
- typically low “EPO-R” expression
- artefficially high concentrations of EPO used
- usually marginal effects
- controversial results

Elliot et al.; Blood 2006;107:1892-1895
Österborg et al.; EJC 2007;43:510-519
Sinclair et al.; Cancer 2007;110:477-488
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Animal experiments

Animal experiments evaluating the effects of rhEPO

- **Improved radio- or chemosensitivity of tumor cells**

Thews et al. 1998	Improved radiosensitivity
Silver et al. 1999	Improved sensitivity to cisplatin
Stüben et al. 2001	Improved radiosensitivity
Thews et al. 2001	Improved sensitivity to cyclophosphamide
Stüben et al. 2003	Improved radiosensitivity
Sigounas et al. 2004	Improved sensitivity to cisplatin, mitomycin C and cyclophosphamide
Golab et al. 2002	Improved response to photodynamic therapy
Ning et al. 2005	Improved radiosensitivity
Tovari et al. 2005	Improved sensitivity to 5-fluorouracil
Shannon et al. 2005	Improved chemosensitivity
Lövey et al. 2007	Improved radiosensitivity
Mittelmann et al. 2001	Improved antitumore immunity and tumor response
Katz et al. 2005	Induced myeloma tumor mass reduction

- **Neither positive nor negative effect**

Hardee et al. 2006	No effect on tumor growth and ist sensitivity to taxol
Kirkpatrick et al. 2006	No effect on tumor growth and radiosensitivity
LaMontagne et al. 2006	No effect on tumor growth and sensitivity to paclitaxel
Geelen et al. 2007	Modulated radiotherapy effect on tumor microvessels

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Animal studies suggest rhEPO improves chemo- and radiosensitivity, reducing tumour progression and improving survival

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Clinical Studies

Clinical studies: Impact of rhEPO on radiotherapy outcome*

- **No negative effect/trend to improvement**

  Rosen et al. 2003, Head and Neck Cancer
  Throuvalas et al. 2004, Cervical and Bladder Cancer
  Machtay et al. 2007, Head and Neck Cancer
  Strauss et al. 2007, Cervical Cancer
  Blohmer et al. 2002, Cervix cancer
  Gupta et al. 2009, Cervix Cancer (Chemoradiotherapy)

- **Reduced survival**

  Henke et al. 2003, Head and Neck Cancer
  Overgaard et al. 2008, Head and Neck Cancer
  Thomas et al. 2008, Cervix Cancer (Chemoradiotherapy)

*randomized trials

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Clinical studies: Impact of rhEPO on chemotherapy outcome

- **Improved or trend to improved outcome**

  Littlewood et al. 2001, Solid Tumors, Hematological Malignancies*
  Vansteenkiste et al. 2002, Lung Cancer *
  Larson et al. 2004, Breast Cancer
  Reed et al. 2005, Ovarian Cancer

- **Neutral/no negative effect**

  Österborg et al. 1996, Lymphoid Malignancies*
  Österborg et al. 2005, Lymphoid Malignancies*
  Grote et al. 2005, Small Cell Lung Cancer*
  Moebus et al. 2007, Breast Cancer*
  Aapro et al. 2008, Breast Cancer*
  Pirker et al. 2008, Lung Cancer*
  Richardson et al 2008, Multiple Myeloma*

- **Reduced survival**

  Leyland-Jones et al. 2005, Breast Cancer*
  Wright et al. 2007, NSCLC (in part chemotherapy)*
  Hedenus et al. 2008, Lymphoproliferative diseases*
  PREPARE study 2008, Breast Cancer*

*** randomized trials.** **Nowrousian M. R.: rhEPO in Clinical Oncology, Springer Wien New York 2008**
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Clinical studies in anemic cancer patients not receiving chemotherapy or radiotherapy

Studies with neutral/positive results:

Mystakidou et al.; Anticancer Res 2005;25:3495-3500
Abels R.; EJC1993;29A:S2-S8
Ludwig et al.; Cancer 1995;76:2319-2329
Shasha et al.; J Support Oncol 2006;4:129-135
Quirt et al.; JCO 2001;19:4126-4134
Johansson et al.; Scand J Urol Nephrol 2001;35:288-294
Charu et al.; The Oncologist 2007;12:723-737
Smith et al.; BJC 2003;88:1851-1858
Gordon et al.; Blood 2006;108:328a (abstr 1304)
Lönnroth et al.; Med Oncol 2008;25:23-29

Study with negative results

Smith et al.; JCO 26:1040-1050, 2008

Target Hb levels in studies showing a detrimental effect of ESA on tumor progression and/or survival

Study	Neoplasm	Treatment	ESA	Target Hb (g/dl)
Henke et al. 2003	Head and neck	Radiotherapy	Epoetin b	> 14 women > 15 men
Hedenus et al. 2003	Lymphoma	Chemotherapy	Darbepoetin a	> 14 women > 15 men
Leyland Jones et al., 2005	Breast	Chemotherapy	Epoetin a	> 14
Wright et al. 2007	Non-small cell lung cancer	Radiotherapy	Epoetin a	> 14
Overgaard et al., 2007	Head and neck	Radiotherapy	Darbepoetin a	> 15.5
PREPARE 2008	Breast	Chemotherapy	Darbepoetin a	> 13
Thomas et al. 2008	Cervix	Chemoradiotherapy	Darbepoetin a	> 14
Smith et al. 2008Treatment	Solid tumors	No antineoplastic	Darbepoetin a	> 13

Hb = hemoglobin; ESA = erythropoiesis-stimulating agent.

Risk of Thromboembolic Event (TE) by Target Hemoglobin Stopping Level (ARHQ)

Target stop hemoglobin (g/dL)	Relative Risk (TE events)	95% Confidence Interval
>12 to ≤13	0.70	0.29 – 1.67
>13 to ≤14	1.71	1.23 – 2.40
>14 to ≤15	1.92	1.22 – 3.02
>15 to ≤16	1.66	1.08 – 2.54

Comparative Effectiveness of Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment AHRQ Technology Assessment 2006

Conclusions

- The „negative“ clinical studies display considerable methodological deficiencies and were performed in settings that are today considered as being inappropriate and/or used unacceptable Hb target ranges.

- When used as indicated, erythropoietic stimulating agents (ESAs) are valuable and safe drugs that do not negatively affect survival.

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ESA Therapy in Clinical Oncology 2009

There is a need for new clinical trials

1. including patients with the same disease, disease stage and risk factors for the outcome of the respective treatment used (radiotherapy, chemotherapy or radiochemotherapy)
2. Using Hb levels ≤ 11 g/dl for initiating treatment
3. Using target Hb levels around 12 g/dl
4. Documenting disease response as well as adverse effects of both ESAs and antineoplastic treatment and, of course, causes of death

Outside of clinical studies, ESAs should be used strictly according to the currently available Giudelines

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