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External radiotherapy and anaemia treatment: state of the art[1]

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Summary

Anaemia is considered a common problem in many cancers secondary to the disease itself or related to chemo- and/or radiotherapy. Several clincal trials have advocated the prognostic value of anaemia and hypoxia in the outcome of many cancers. Erythropoietin is recognised as an effective treatment for anaemia, which also improves the quality of life in patients with malignant disease. External radiotherapy plays an important role in the treatment of loco-regional cancer but its efficacy can be compromised by many factors. Tumor hypoxia is considered by many authors as an important factor contributing to radioresistance. We report in this article the radiobiological rationale in favour of combining radiotherapy and erythropoietin, and review relavant clinical papers published in this field.

Key words: anaemia, radiotherapy, erythropoietin

Introduction

Anaemia is commonly seen in a variety of cancers at various stages of progression. It may be secondary to the cancer or associated with myelotoxic regimens such as chemotherapy and/or external radiotherapy [1–3].

The prevalence and effects of anaemia were long disregarded by oncologists. Over the last few years, numerous papers reporting from this field have pointed out the prognostic value of anaemia and the adverse effects of tumour hypoxia on the efficacy of anticancer treatments, in this way promoting resistance to radiotherapy and/or chemotherapy.

Retrospective studies show that patients with satisfactory haemoglobin levels receiving external radiotherapy primarily for cancers of the cervix [4–6] and head and neck cancers [7–9] have better loco-regional tumour control and better overall survival.

External radiotherapy is of paramount importance in loco-regional cancer treatment. Its success may be compromised by the presence of demonstrably unfavourable factors such as tissue hypoxia and a low haemoglobin level [10–12].

In combination with iron supplementation, recombinant human erythropoietin (rhuEPO) is recognised as effective for treating anaemia in cancer patients on chemotherapy. The use of rhuEPO has been demonstrated to have a sustained beneficial impact on patient quality of life [13–17]. It has been studied in randomised phase I/II and phase III trials in combination with external radiotherapy with or without chemotherapy by a number of research teams. A recently published study describes the beneficial impact of a weekly dose of 40000 IU of rhuEPO on quality of life in chemoradiotherapy recipients [18].

This paper presents radiobiological arguments in favour of combining external radiotherapy and rhuEPO and provides a critical review of clinical papers published in this field.

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Radiobiological rationale

Most radio-oncology departments use linear accelerators producing indirectly ionising X rays. Passing through matter, the radiation provokes a series of physicochemical reactions caused by water radiolysis, giving rise to the formation of free radicals which, in the presence of oxygen, fixes the damage in tumour cells by breaking double-stranded DNA [19]. Oxygen must be present in sufficient quantities in the intracellular milieu during irradiation in order to act as a powerful sensitiser of cells to the effects of radiation. Hence, the extent of the biological effect of radiotherapy correlates positively with the oxygen concentration.

Research work by Thomlinson and Gray in the 1950s showed that hypoxia is a factor involved in radiation tolerance [20]. The external radiotherapy (RT) doses must be multiplied by a factor of 3 to eradicate hypoxic tumour cells and thus to obtain the same biological effect versus normally oxygenated cells. This phenomenon is known by the term oxygen enhancement ratio (OER) [19].

Anaemia plays a complex role in the interaction between tumour hypoxia and stimulation of angiogenesis. Hypoxia induces the expression of various angiogenic cytokines (VEGF, bFGF, IL-8, TNF, etc), responsible in the course of various signal transduction cascades for the proliferation, migration and differentiation of the endothelial cells responsible for the development of neovasculature in a tumour. As the tumour increases in size, so do the hypoxic areas and the angiogenic signals responsible for development and metastasis increase [21].

On the basis of experimental models, it is suggested that tumour hypoxia in the tissues arises when partial oxygen pressure in the venous end of capillaries declines below 45–50 mm Hg [22]. To demonstrate the correlation between anaemia and hypoxia, Groebe et al., having validated the pertinent parameters – including blood flow, arterial partial pressure (90–100 mm Hg) at a haemoglobin level of 14 g/dl – were able to induce arterial hypoxia and raise hypoxia levels in tumour tissue in the presence of haemoglobin levels below 10 g/dl [23].

Hypoxia, therefore, induces cell resistance mechanisms both to radiotherapy as indicated above, and also to chemotherapy agents. Hypoxia gives rise to inhibition of cellular proliferation by an accumulation of cells in phase G0 of the cell cycle. It reduces cytotoxicity, induces hypoxic stress proteins, lowers the apoptotic potential and causes tissue acidosis [24].

Hypoxia was recently shown to be responsible for increasing the instability of tumour cell DNA, resulting in the development of cell clones with a low apoptotic potential and high metastatic potential [25–27].

This narrow link between tumour oxygenation and haemoglobin levels is proof of the importance of treating anaemia. Rectification of this anaemia before or during external RT with curative-intent might help to increase loco-regional control of the cancer and, in the best of cases, improve overall survival.

Ways to overcome tumour hypoxia and anaemia during radiotherapy

Blood transfusion prior to irradiation was the traditional approach to rectifying anaemia, but various studies have failed to disclose a significant effect in spite of increased haemoglobin concentrations [28]. Overgaard et al. conducted a randomised trial to investigate the effects of a radiosensitiser (nimorazole) and evaluate the rectification of anaemia by blood transfusions in patients with head and neck cancers [29]. The authors observed a statistically significant correlation between the pre-radiotherapy haemoglobin level and local tumour control. On the other hand, no difference was found in terms of local control between transfused (39%) and non-transfused subjects (35%). The authors explained these results by the fact that tumour growth starts before irradiation and postulated the advisability of progressively raising the haemoglobin level during radiotherapy. The results indicate the importance of stratifying patients according to their baseline haemoglobin level in future randomised trials.

Other studies were based on the concept of combining different hypoxia-modifying agents during curative-intent irradiation of head and neck cancers [29–31]. A Danish group conducted several *in vitro* and *in vivo* studies on a number of radiosensitising agents. In the DAHANCA protocol 5–85, nimorazole displayed benefits both in terms of local control and disease-free survival in cancers of the pharynx and larynx [29]. Lee et al. investigated the role of etanidazole in a randomised study involving subjects with head and neck cancer [31]. The fate of 289 patients was reported in relation to their baseline haemoglobin levels prior to irradiation. Five-year survival was 36% in the non-anaemic group versus 22% in the anaemic group. Other drugs (metronidazole) have been abandoned because of their peripheral neurotoxicity [32].

Although hyperbaric oxygenation has the potential to improve response to radiotherapy, as demonstrated in experimental tumour models [33], logistics and technical difficulties limit the routine use of hyperbaric oxygen in radiotherapy

[34]. In our view similar difficulties hamper the routine use of artificial blood in anaemic cancer patients undergoing radiotherapy.

Agents that either reduce the oxygen binding capacity of haemoglobin (eg, efaproxiral) or modify the haemorrheologic characteristics (eg, pentoxifylline) have shown the potential to increase tissue oxygenation and radiosensitivity [35, 36]. However, extensive clinical data are lacking.

The use of rhuEPO in combination with iron in the treatment of anaemia has emerged as a new alternative approach capable of gradually increasing the haemoglobin level before and/or during radiotherapy [37, 38].

Combination of external radiotherapy (RT), erythropoietin (rhuEPO) and iron

Phase I-II clinical trials

The first phase I trial was reported by Lavey et al. from the University of California, Los Angeles and involved forty non-metastatic patients presenting with different types of localised supradiaphragmatic cancers [39]. Subjects with a haemoglobin level below 13.5 g/dl and scheduled to undergo external radiotherapy (RT) for a period of 5 to 8 weeks were eligible for the study. Recombinant huEPO (epoetin alfa) was injected subcutaneously at a dose of 150–300 IU/kg three times a week. This treatment was administered for 10 days before starting RT in a group of 20 patients. The other group served as a control arm. The entire study population received iron sulphate supplementation per os. This study demonstrated a 6% increase in haemoglobin level during RT in the rhuEPO group, rising from 11.9 ± 1.3 to more than 14 g/dl in 80% of subjects in the rhuEPO group versus 5% in the control arm. Recombinant huEPO was excellently tolerated.

Vijayakumar et al. carried out a randomised phase II study in 26 patients with various solid tumours (lungs, breast, cervix and prostate). The first group received radiochemotherapy on its own (to match their primary tumour), and the second group received rhuEPO in addition (epoetin alfa; 200 IU/kg Monday to Friday) and iron sulphate per os. The protocol permitted reducing the dose to 100 IU/kg if haemoglobin levels rose above 15 g/dl in men and above 14 g/dl in women. In the 2nd group, haemoglobin levels rose by 0.43 g/dl per week. The authors recommend administering rhuEPO several weeks before starting radiotherapy [40].

Dusenbery et al. evaluated the efficacy of rhuEPO (epoetin alfa) in 20 patients with resected epidermoid carcinoma of the cervix and haemoglobin levels below 12.5 g/dl [41]. rhuEPO was administered at a dose of 200 IU/kg/day in combination with iron sulphate. This treatment was started 5–10 days before initiating RT. The results show a 30% increase in haemoglobin levels during RT in the rhuEPO group, rising from 10.3 ± 1.04 to 13.2 ± 1.7 g/dl. Two patients developed deep vein thrombosis as a side effect 9 to 10 days after finishing RT treatment and rhuEPO.

Henke et al. randomised 50 patients with head and neck or cervical cancer to one of four different rhuEPO dosing regimens (epoetin alfa or epoetin beta; 150 IU/kg week i.v., 300 IU/kg/week i.v., 150 IU/kg/week s.c., and one group with no treatment). Haemoglobin levels rose 0.7 g/dl/week in rhuEPO recipients with a significant correlation between the increase in haemoglobin levels and local control regardless of the specific rhuEPO dosing regimen [42].

In these prospective clinical trials, rhuEPO administered at a dose of between 150 and 300 IU/kg 3 times per week in combination with iron substitution (strict supplementation) is effective in achieving a haemoglobin level of 12 to 14 g/dl during external RT in 80% of patients. Tolerance is acceptable apart from rare cutaneous reactions (at the injection site) and rare deep venous thrombosis, mainly at haemoglobin-levels exceeding the recommended target level of 12 g/dl [43].

Phase III clinical trials

Glaser et al. performed an uncontrolled trial in 60 patients diagnosed with T2–4 N0–2 cancers of the oral cavity and haemoglobin levels below 12.5 g/dl [44]. The treatment was composed of a combination of external RT (total dose of 50 Gy) and chemotherapy (mitomycin C and 5-fluorouracil) followed by surgery at week 10. One arm received rhuEPO (epoetin alfa) at a dose of 150 IU/kg s.c. three times per week. The protocol

Table 1

Certain demographic characteristics of patients in Henke's study [47].

	epoetin beta n (%)	placebo n (%)
Sex (male)	158 (88%)	145 (85%)
Smokers*	118 (66%)	91 (53%)
Hypopharynx	40 (22%)	43 (25%)
Stage III (AJCC)	37 (21%)	46 (27%)
Stage IV (AJCC)	135 (75%)	123 (72%)
Relapsed patients	18 (10%)	13 (8%)

*p <0.05 (significantly more smokers in the epoetin beta group).

Table 2

Characteristics of the subgroup of patients with cancer of the hypopharynx in Henke's study [47].

	epoetin beta arm (n = 40)	placebo arm (n = 43)
Sex (male)	90%	86%
Smokers	55%	44%
Stage IV (AJCC)	85%	70%
Relapsed patients	15%	8%

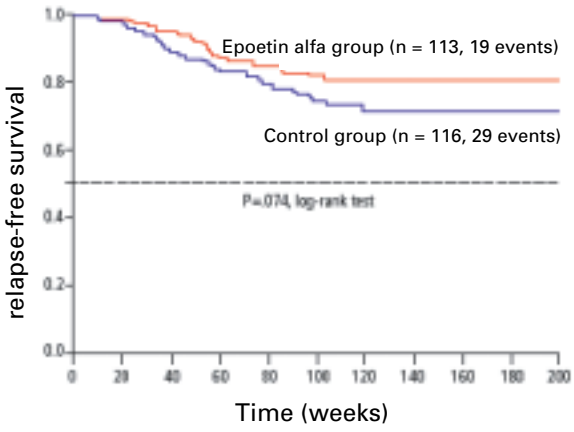

Figure 1

Recurrence-free survival in subjects with high-risk cervical cancer on chemotherapy receiving transfusions or epoetin alfa for treatment of anaemia [46] (reproduced with permission).

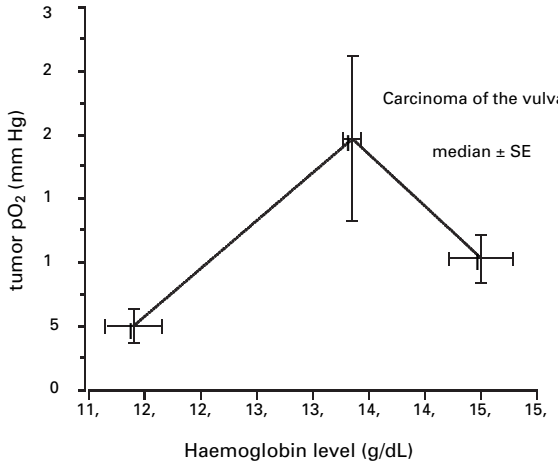

Figure 2

Haemoglobin level and tumour oxygenation: optimum tumour oxygenation in carcinoma of the vulva is obtained in subjects with a haemoglobin level of 13.8 g/dl [52] (reproduced with permission).

allowed the dose to be doubled in subjects whose weekly haemoglobin increase was below 0.3 g/dl. No iron supplementation was prescribed in this study. The complete response rate after neoadjuvant treatment was 63% in the rhuEPO group versus 27% in the non-rhuEPO group. Overall survival (90% vs. 60%; p = 0.03) and loco-regional control (90% vs. 63%; p = 0.03) at 2 years were significantly superior in the rhuEPO arm. This was the first study to show the efficacy of rhuEPO in combination with neoadjuvant radiochemotherapy but the control arm was based on comparison with a historical cohort.

The same Viennese group published the results of a retrospective study in 191 patients which probably included the data from the controlled trial described above [45].

A study reported by Blohmer et al. [46] investigated the impact of rhuEPO combined with iron in high-risk patients with cervical cancer. The patients underwent hysterectomy followed by radiochemotherapy combined with epoetin alfa (3×10000 IU/week) versus standard care and transfusions as needed. rhuEPO treatment reduced the number of anaemic patients (p = 0.001) and lowered the number of transfusions (p <0.02) and kept haemoglobin levels above 12 g/dl despite radiochemotherapy. The relapse rate was lower in the rhuEPO arm (17% versus 25%, p <0.07) than in the control arm. This is shown in figure 1.

A phase III trial testing the efficacy of combined rhuEPO (epoetin beta) and external RT was recently published [47]. Henke et al. randomised 351 patients with epidermoid carcinoma located in the oral cavity, oropharynx, hypopharynx or larynx with haemoglobin levels below 12.0 g/dl (for women) or 13.0 g/dl (for men). Subjects with external curative-intent RT (postoperative or on its own) were eligible to take part in this randomised, multicentre, double-blind trial. The first group of 180 patients received epoetin beta at a dose of 300 IU/kg s.c. 3 times per week, administered from day 14 to day 10 before RT, during and upon completion of irradiation. The other group of 171 patients received placebo by the subcutaneous route. The study prescribed weekly iron supplementation by the intravenous route (200 mg of iron saccharate or 187.5 mg of iron gluconate) in subjects with a transferrin saturation remaining below 25%, or, alternatively, iron supplementation by mouth. None of the patients received chemotherapy. Loco-regional progression-free survival was the primary endpoint of the study. Time to loco-regional progression and overall survival were evaluated as secondary endpoints in this trial.

The results of this study were surprising in that, despite an increase in haemoglobin levels to >14 g/dl in women and >15 g/dl in men, the various outcome measures analysed – namely, loco-regional progression-free survival, time to progression, and overall survival – were inferior in the experimental arm.

A number of points have been raised in connection with this trial [48]. Firstly, the results were negative and indeed contradictory compared with studies conducted by other teams. Secondly, 58/171 (34%) of the placebo patients and 79/180 (56%) of the EPO group were protocol violators. Only 73% of the total study population were treated as stipulated in the protocol. The results obtained in the patients abiding by the protocol revealed no difference as regards survival or loco-regional control. Thirdly, TNM grading and performance index of the patients involved were not described by the authors though these are predictive of prognosis in head and neck cancers. Finally, an imbalance between the two arms was probably a crucial factor in this study. Table 1 outlines the various characteristics of the patients in this trial and shows that the epoetin beta group contained a significantly higher percentage of smokers in comparison with the control group. Recent publications report the presence of higher risk cancers in smokers [49] and poorer survival rates in cancer patients who continue smoking during chemoradiotherapy [50]. The latter observation could be related to the fact that carboxyhaemoglobin, found in increased concentrations in the blood of smokers, reduces the amount of oxygen that can be carried to the tissues, thereby increasing tumour hypoxia and reducing the effectiveness of ionising irradiation [51]. Table 2 summarises the characteristics of the subgroups of patients with cancer of the hypopharynx, a localisation known to be asso-

ciated with a worse prognosis than other head and neck cancer sites. The percentage of smokers, subjects with stage IV disease and relapse was higher in the epoetin beta group than in the placebo group. The presence of these risk factors in subjects with hypopharyngeal cancer in the epoetin beta group probably caused an imbalance between the two groups which would explain the negative impact in the rhuEPO treatment arm. Regrettably, the subgroup analysis was not initially scheduled in this trial. Owing to the limited number of patients analysed in these subgroups, no significant conclusions can be drawn. The median haemoglobin level rose from 11.7 g/dl to a mean level of 14.8 g/dl at 4 weeks in the epoetin beta group, possibly explaining a higher incidence of vascular complications (hypertension, haemorrhage, venous thrombosis, pulmonary embolism and cerebrovascular accidents) in the epoetin beta group (11% versus 5%). In general, major toxicity was comparable in the two study arms (8% in the rhuEPO arm versus 6% in the placebo arm). There were also 10 cardiac deaths in the experimental arm compared to 5 in the placebo arm [47]. Is epoetin beta justified in patients with haemoglobin levels above 14.0 g/dl who are not receiving treatments known to be myelotoxic?

The authors conclude that: 1) Despite the increase in haemoglobin levels, treatment with rhuEPO demonstrated no impact on loco-regional progression-free survival, loco-regional progression, and global survival in an intent-to-treat analysis (excluding no patients) in subjects with head and neck cancer; 2) this study does not confirm the hypothesis of a radiosensitising effect of rhuEPO, and 3) more studies are necessary in order to analyse the effect of rhuEPO treatment on cancer control and survival [47].

This study came in for widespread criticism, as evidenced by the number of letters to the editor in response to its publication [48]. Although the points raised by the various authors have been outlined above, we would nevertheless like to present in greater detail the hypothesis supported by Vaupel et al. regarding a link between haemoglobin levels and intratumoral pO_2 [52]. The latter authors showed that optimum intratumoral oxygenation in patients with gynaecological cancers is associated with haemoglobin levels ranging from 12 to 14 g/dl (fig. 2). Haemoglobin levels above 14 g/dl are associated with a decline in tumour oxygenation, probably attributable to declining blood perfusion owing to higher viscosity. Extrapolation of the hypothesis tendered by Vaupel et al. [52] to the results of the study by Henke et al. [47] provides a likely explanation for the harmful effect seen in the rhuEPO arm. The patients in the placebo arm had a median haemoglobin level of 12.9 g/dl compared with 15.4 g/dl in the experimental arm. The haemoglobin concentration achieved in the placebo arm would have been sufficient if the aim of the study were to reduce the hypoxic fraction of the tumour. Any additional rise in haemoglobin levels might have compromised the beneficial effect. The role and function of EPO receptors is unknown at this time. Studies are under way to investigate the effect of rhuEPO on tumour cell lines expressing EPO receptors. New clinical trials would be desirable to answer this question.

Limitations to the use of rhuEPO?

The additional cost of using rhuEPO to treat anaemia in cancer patients undergoing external radiotherapy has not been specifically addressed so far. When comparing the use of rhuEPO to red blood cell transfusions, however, a study by Cremieux et al. [53] indicated that rhuEPO (in conjunction with transfusion) may be about 20% more cost effective than transfusions alone (in terms of the cost to achieve a specified improvement in haemoglobin-level). In addition, rhuEPO can prevent the occurrence of anaemia in many non-anaemic patients with cancer and at risk of developing anaemia under treatment. These patients would normally not be transfused unless the haemoglobin-level has dropped to low levels, eg, <8 g/dL. In contrast to the current "best standard of care", including red-blood cell transfusions as needed, the use of rhuEPO results in sustained improvements in quality of life, whereas the effect of transfusions is not sustained beyond 2 weeks [16, 17]. Finally, it has to be taken into account that the supply of donor blood is limited. The recent intervention of the Swiss health authorities aiming at a prevention of the spread of variant Creutzfeldt-Jacob disease through blood donors will increase the shortage of donated blood, necessitating its restricted use in carefully selected patients.

In the year 2002, the rare occurrence of antibody-mediated pure red cell aplasia (PRCA) in patients suffering from renal insufficiency and undergoing treatment with rhuEPO was reported [54]. It is known from the literature that all exogenously dosed proteins can induce an immunogenic response with antibody production, especially when given subcutaneously [55]. RhuEPO-induced PRCA in patients with renal insufficiency has been reported worldwide and with all rhuEPO-products and preparations. For epoetin alfa, a temporary increase in PRCA-incidence in patients with renal insufficiency was observed since 1998 with a peak in 2002 [54]. For (radio-) oncologists it is important to note that despite intense surveillance, no cases of PRCA in the other registered indications of epoetin alfa, eg, in oncol-

ogy, have been reported. Several measures were taken (eg, intravenous administration in patients with renal insufficiency), and an investigation was started to identify the cause of this phenomenon. Recently the most likely cause was identified: chemicals released from the rubber stoppers of prefilled syringes acted as an immunological adjuvant [56]. The rubber stoppers were only used for epoetin alfa syringes (outside the USA) and they have been replaced by Teflon stoppers. The PRCA-incidence for epoetin alfa in patients with renal insufficiency is again at the very low level reported until 1998.

Conclusions

Recombinant-huEPO in combination with iron is definitely effective in treating anaemia during chemotherapy or radiochemotherapy in subjects with solid tumours.

The improvement of loco-regional control of head and neck cancers achieved by RT depends on a number of prognostic factors, including the underlying tumour, tissue environment, and patient on the one hand, and, on the other hand, various factors concerned with the irradiation process itself.

In experimental models, treating anaemia with rhuEPO improves tumour response to radiation treatment [57–60]. The same applies to cytotoxic treatment such as cyclophosphamide whose action depends on the presence of oxygen, where rhuEPO restores chemosensitivity [61].

A phase III prospective study launched by EORTC (22996) was intended to randomise subjects with head and neck cancer treated with RT alone to receive rhuEPO-based treatment versus placebo. We regret the early termination of this study due to inadequate recruitment, as it would have answered some of the questions raised above. The role of combination rhuEPO-external radiotherapy remains inconclusive; new clinical trials based on clearly defined criteria are required to demonstrate its importance.

In the meantime, treatment of treatment- or tumour-related, symptomatic anaemia using blood transfusion and/or rhuEPO remain still an appropriate means of enhancing the quality of life of cancer patients.

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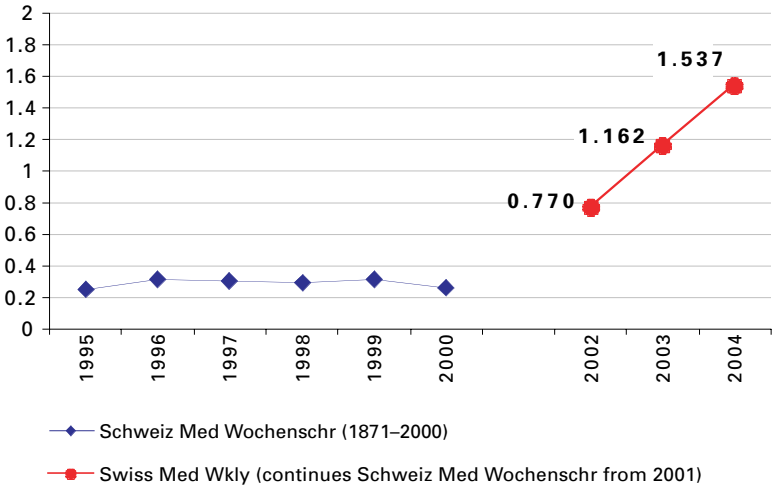

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