Annals of Case Reports
Rhomberg W. Ann Case Rep: 8: 1150
www.doi.org/10.29011/2574-7754.101150
www.gavinpublishers.com

Case Report

Successful Treatment of a Malignant Hemangioendothelioma of the Thyroid with Metastasis to the Lung. A Case Report

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Citation: Rhomberg W (2023) Successful Treatment of a Malignant Hemangioendothelioma of the Thyroid with Metastasis to the Lung. A Case Report. Ann Case Report. 8: 1150. DOI:10.29011/2574-7754.101150

Received: 26 January 2023, **Accepted:** 31 January 2023, **Published:** 02 February 2023

Abstract

The malignant hemangioendothelioma of the thyroid is a rare disease, which occurs mainly in the Alpine regions but not only there. It affects elderly patients with a history of goitre and has a fatal course in the majority of patients. This report describes the case of a 75-year-old man who suffered from a malignant hemangioendothelioma of the thyroid metastatic to the left lung. Treatment with metronomic doses of vindesine and razoxane and radiation therapy of the metastasis as well as the thyroid region rendered the patient disease-free. He received a maintenance therapy with vindesine and razoxane over three years. The patient survived ten years with a disease condition which is usually rapidly lethal. The reason to publish this case report is to remind people of a drug that has several amazing abilities and was largely ignored by the medical community. The drug `razoxane´ has not been on the market for several years. However, it could still be used again in the form of its racemic enantiomer `dexrazoxane´ which is approved as a cardio protectant in the context of a treatment with doxorubicin, or in extravasations.

Case Report

B.J., a 75 year old internal revenue officer suffered from a malignant hemangioendothelioma of the thyroid, a rare disease, which is mainly seen in Alpine regions where goitre may be endemic. The diagnosis was made in March 1996 and a left sided thyroidectomy was performed as primary treatment. The tumour was histologically proven as malignant hemangioendothelioma of the thyroid (factor VIII positive), grade 3. Radiation treatment of the thyroid was initiated concurrently with razoxane per os. Shortly thereafter, a haemoptysis occurred due to metastasis of the left lower lobe of the lung (Figure 1) with bleeding into the surrounding lung tissue. At this point, the life expectancy of those patients is usually 2-3 weeks. Treatment was started with metronomic doses of vindesine (2 mg intravenously weekly) and razoxane (initially 2 x 125 mg per os daily, five times per week). Further treatment details: see reference [1]. Radiation therapy at the metastatic region was added three days after the first razoxane dose. The planned radiation dose was 50 Gy using small fields. Four weeks later (after about 30 Gy) a chest X-ray control showed already a subtotal regression of the metastasis, the bleedings have been resorbed (Figure 2). A complete regression of the lesion was finally achieved followed by a focal pneumonitis leading to intermittent cough of moderate degree. A maintenance treatment with metronomic doses of razoxane and vindesine was then given over three years. The further course of the disease was not remarkable, and the patient was alive at 120+ months with no evidence of disease at further follow up.

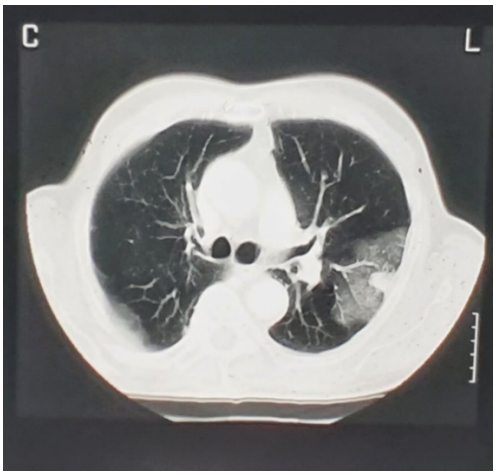

Figure 1: Sessile metastasis of the left lung (size about 1.5 cm) with bleeding into the surrounding lung tissue. Pleural residuals after tuberculosis are seen at the right side. (November 11, 1996).

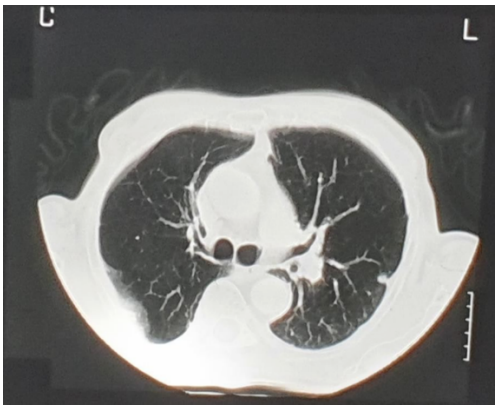

Figure 2: CT-scan of the chest, December 10, 1996. Partial regression of the metastatic nodule after about 30 Gy. The bleedings have been resorbed.

Discussion

The main reason to publish this case report was not only to remind people of the unique drug 'razoxane' which is still not available for treatment but also to indicate that dexrazoxane could certainly be used instead of razoxane to achieve similar effects, especially to inhibit or to delay the metastatic process which is usually dominating not only in angiosarcomas but also in certain other carcinomas and sarcomas.

Modes of action of razoxane

Razoxane has an intriguing and fascinating spectrum of activities. It blocks the cell cycle in the G2- and early M-phase [2]. Since the G2/M phase is the most sensitive phase to ionizing irradiation, a block of the cell cycle in this phase might be one reason why the drug exhibits a strong radio sensitizing ability in animal experiments and in the clinic. Besides the radio sensitizing ability, razoxane has an outstanding potency to inhibit metastasis. No other drug suppresses metastasis in animal tumours more effectively than razoxane [3]. Several reasons may be responsible to this phenomenon. For instance, there is an effect of razoxane on the invasion of tumour cells to which little attention was given. Although razoxane is not a tubulin-affinic drug and therefore, does not touch cellular motility and deformability, Karakiulakis et al. observed that the drug is able to inhibit the collagen-degradation of basement membrane induced by a malignant tumour enzyme [4]. Some years earlier, Duncan and Reynolds already observed that the collagenase production was inhibited and TIMP (tissue inhibitor of metallo-proteinase) was increased by razoxane [5]. A suppression of up-regulation of gelatinases was later described by Garbisia et al. and linked to the suppression of metastasis [6]. Welch et al. confirmed an anti-invasive potential of razoxane in the membrane invasion culture system (MICS) [7]. The anti-invasive mode of action of razoxane is rarely mentioned in the literature, yet it probably represents a further mechanism which supports our understanding of the marked antimetastatic activity of the drug. Other modes of action of razoxane are the inhibition of DNA topoisomerase II, first described by Tanabe et al. 1991 [8], or the interesting chelation of metals due to the fact that bis-diketo-piperazines (e.g., razoxane) are derivatives of EDTA (ethylenediamine tetra-acetic acid). Those results must be read in detail in the monograph on razoxane and dexrazoxane [3].

The normalization of pathological tumour blood vessels

In view of the presented case report, however, a closer look must be given to one of the most interesting activities of razoxane, i.e., its ability to normalize pathological blood vessels in experimental tumours. This was first shown in transplanted Lewis lung tumours (LLC) in mice [9-11]. The same phenomenon was observed in a hamster lymphoma model [12]. It was hypothesized and concluded that this unique `blood vessel normalizing activity´ could be the key to prevent distant metastases. Figure 3 shows the macroscopic aspects of these experiments.

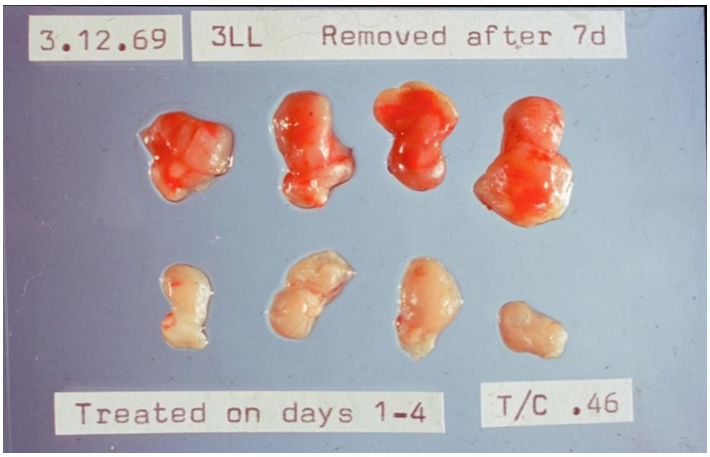

Figure 3: Lewis lung tumour (3LL) implanted subcutaneously and treated with 30 mg/kg razoxane i.p. daily for 4 days from day of implant. Tumours excised on day 7 and lungs examined 2 weeks later. Normalization of the tumour vasculature reduced haemorrhages and lung metastases [11].

The discovery that razoxane could comprehensively reduce 3LL metastases without significant inhibition of the growth of the primary implant was interesting in a number of ways. Not only did it achieve for the first time the obviously desirable therapeutic goal of preventing tumour spread, but perhaps more interesting was the demonstration that it was possible to delete one malignant characteristic, the most lethal one, without markedly affecting others such as uncontrolled proliferation. Analysis of the mechanism of the anti-metastatic action of razoxane revealed that it was due to changes the drug induced in the primary tumour implant. In contrast to the controls, no tumour cells or fragments of them were detectable in the blood of the treated mice [13]. Indeed, when razoxane (Rz) was clinically tested as cytotoxic agent, it was observed in randomized studies that even when there were fewer objective responses in the group treated with Rz compared to a control group receiving a different treatment, there still was a survival benefit in patients who received razoxane. This interesting and seemingly paradoxical phenomenon should further be elucidated. The histological examination of 3 LL tumour implants shows the normalization of pathologic tumour vasculature (Figure 4a and b).

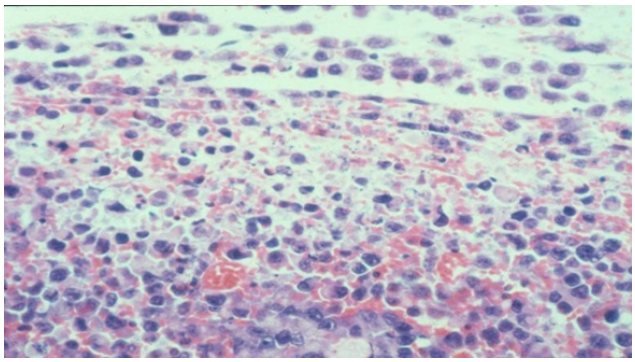

Figure 4a: Tumour implants of animals (Lewis lung carcinoma) without pre-treatment by razoxane. The tumours are haemorrhagic, the blood vessels are poorly endothelialized and tortuously sinusoidal. All tumours metastasize to the lung.

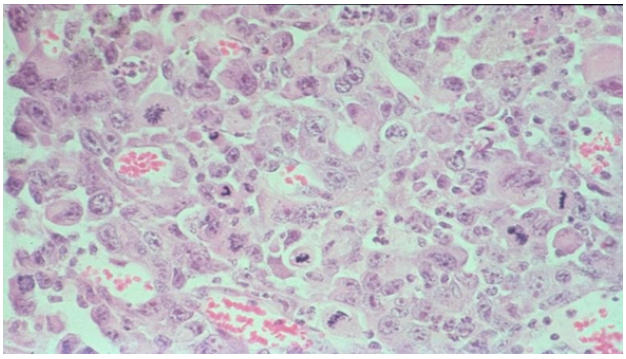

Figure 4b: Lewis lung carcinoma implant after pretreatment by razoxane. Now endothelialized blood vessels are seen and there is no evidence of leakiness [14]. There were no metastases in the lung!

Some future aspects

Unfortunately, razoxane has not been commercially available for years, but dexrazoxane (DXR) is used in therapies with doxorubicin for prophylaxis of cardiac injury (trade name Cardioxane®). The drug is still topical; and recently long-term results have been published on it [15]. DXR is also used to treat extravasations of doxorubicin under the trade name Savene®. Both Cardioxane® and Savene® are approved by the EMA (European

Medicines Agency) and available in pharmacies. In our judgment, attempts should be made to repeat certain studies or therapeutic applications with dexrazoxane instead of razoxane. Where would the comparable, optimal doses for dexrazoxane (DXR) be? Dose-finding studies would certainly be needed to some extent; possibly low (metronomic) doses would be sufficient to reproduce the amazing effects observed with razoxane. Thus, it has come to the author´s attention that 50 mg of DXR weekly and low doses of a Vinka alkaloid together with radiation therapy were sufficient to place a small inoperable angiosarcoma of the scalp in complete remission [16].

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