

Magnetic-mediated Mitoxantrone in Cancer Treatment: *In Vivo* Dosage and Application in a Critical Case

Krukemeyer MG^{1*}, Krenn V², Wagner W¹ and Resch R³

¹Department of Radio-Oncology, Paracelsus-Hospital, Sedanstr, Osnabrück, Germany

²Centre of Histology, Cytology and Molecular Diagnostics, Germany

³University of Trauma Surgery and Sports Traumatology, Mullner Hauptstrasse, Austria

Introduction

Cancer plays an increasing role in present-day health care systems, mainly due to longer life expectancies. However, cancer treatment remains a difficult challenge despite growing therapeutic progress. One of the difficulties in successfully tackling tumors is related to the serious side effects of anti-tumor drugs on non-malignant body tissue. A progressive method to overcome this bias may increasingly be provided by using magnetized nanoparticle complexes, either excluding or including hyperthermia [1-3].

Previously, we reported on a promising mitoxantrone therapy by magnetic targeting in a murine tumor model and the successful application in a female patient [4]. Here we present an extension of this approach by investigating dosage effects *in vivo* and its application in a male patient. In this extreme, multi-metastasized case a palliative treatment the approach had to be taken.

Materials, Methods and Results

Animal studies

Wag/Rij rats were contaminated by implantation of a rhabdomyosarcoma by injection. Cytostatic mitoxantrone bonded to iron oxides [Fe₃O₄] was administered intravenously into a vein or artery. The laboratory data referring to the used nanodrug are presented in Table 1. A magnetic field strength of 0.6tesla was applied externally but close to the infected body area. The activity measured was 0.31tesla at 3 mm depth, and 0.03tesla at 10 mm depth respectively.

This procedure was repeated at different rates according to the respective experimental group, resulting in varying dosage amounts

Product-No.	05-02-252S
Product-Name	nanomag-CLD
Product description	magnetite dextran composite particles, cross-linked, COOH modified
Surface	Mitoxantron (10 µg/mg)
Size	250 nm
Solid content	10 mg/ml
Iron content	>57% (w/w), corresponds to >79% (w/w) magnetite
Quantity	10 ml
Polydispersity index	<0.2
Shape	cluster-type
Density	2.5 g/ccm
Magnetization	43 emu/g particles (H=1000 Oe)
Saturation magnetization	>67 emu/g particles (H>10.000 Oe)
Stable in	aqueous buffers pH>4
Not stable in	organic solvents, acidic solutions pH<4
Product form	suspension in 0.9% saline
Particles per ml	3.0 × 10 ¹¹
Partciles per mg	3.0 × 10 ¹⁰
Additional remarks	Storage at 4°C for 3 months, do not freeze

Table 1: Detailed dates of the nanodrug used [micromod].

(Table 2). Tumor volumes were determined at treatment start (day 1) and seven days later (day 8).

Results: Tumor growth was highly significantly reduced even with the lowest mitoxantrone dosage application (Group VIII, p=0.0087; Table 3). However, absolute tumor volume reduction (compared to day 1) was achieved only in Groups IX and X respectively (Tables 3-5). Interestingly, no significant difference in tumor reduction could be found between these two groups, i.e. the groups with the middle and highest drug dose.

The fact that the low dosage group (VIII) responded positively to magnetically mediated mitoxantrone becomes more apparent when comparing the (more reliable) median value with the control group median. In this case, absolute tumor size was proven to be smaller for Group VIII at borderline significance (p=0.0519).

Individuals clearly differed to some extent in tumor volumes, although not significantly, in all groups. This in no way affected the clear-cut inter-group differences in tumor development.

Human study

In a 65-year-old man a highly malignant pleomorphic sarcoma on the right upper arm detected in February 2009 developed a polymetastatic syndrome (local ulcerous relapse; skeleton and lung metastases), but no liver metastases. Further diagnosis was adiposity and leg edema connected with stasis dermatitis (170 cm, 97 kg). After three conventional therapy approaches (150 mg doxorubicin, 4,000 mg oxazaphosphorine i.v., 45 Gy radiotherapy), a large pre- and retrosternal metastasis was treated in October 2009 by magnetic drug-targeting. The total drug dosage was 100 mg mitoxantrone (i.e. starting with 2 times 20 mg on 2 consecutive days, after a two-week pause 3 times 20 mg within 4 days). Method of close magnetic administration: see Animal study.

Results: MRI showed a large solid, non-movable, T2-dominated presternal metastasis situated subcutaneously and covering an area of 115 × 85 × 65 [mm]=635,375 mm³ before treatment (Figure 1). Five days after the final application day (i.e. after an 18-day treatment period), the metastasis had shrunk dramatically to 84 × 57 × 41 [mm]=196,308

***Corresponding author:** Krukemeyer MG, Department of Radio-Oncology, Paracelsus-Hospital, Sedanstr 109, D49076 Osnabrück, Germany, Tel: 49070529250; E-Mail: dr-krukemeyer@t-online.de

Received August 17, 2015; **Accepted** September 10, 2015; **Published** December 01, 2015

Citation: Krukemeyer MG, Krenn V, Wagner W, Resch R (2015) Magnetic-mediated Mitoxantrone in Cancer Treatment: *In Vivo* Dosage and Application in a Critical Case. J Nanomed Nanotechnol 6: 330. doi:10.4172/2157-7439.1000330

Copyright: © 2015 Krukemeyer MG, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Group	Operative measure	Total duration [*] each administration 30 min	Subjects (n)
VII	4 × 0.5 mg/kg NaCl ^{**} (control group)	>2 h	6
VIII	4 × 0.5 mg/kg BW MagnaDrug Mitoxantrone ^{**} in a magnetic field	>2 h	6
IX	6 × 0.5 mg/kg BW MagnaDrug Mitoxantrone ^{**} in a magnetic field	>3 h	6
X	8 × 0.5 mg/kg BW MagnaDrug Mitoxantrone ^{**} in a magnetic field	>4 h	6
Total number			24

^{*}duration of magnetic field exposure ^{**}slow intravenous injection>5 min

Table 2: Study groups in dose-effect tests.

	N (Day 1/Day 8)	Day 1 mean ± SD	Day 8 mean ± SD	Difference (of means)
VII	6/6	9605.15 ± 3789.03	20816.27 ± 5006.76	11211.12
VIII	7/4 ^{**}	11589.22 ± 1756.67	13900.22 ± 4113.67	2510.99
IX	6/6	9320.15 ± 1665.68	7173.54 ± 1762.24	-2146.61
X	5/4 ^{**}	10643.59 ± 2085.07	8026.63 ± 1908.76	-3127.61

*1 subject transferred from Group X to Group VIII because treatment conforms to VIII

**2 subjects deceased in group VIII, another one in Group X

Table 3: Tumor volume development (in mm³) in the dosage-efficacy tests.

	Group VII	Group VIII	Group IX	Group X
Difference (mm ³)	11836.32	3179.50	-2306.57	-3752.39
p value	0.0313	0.1875	0.0313	0.2500

p values<0.05 in **bold**

Table 4: Dose-effect study. Intra-group comparisons for tumor volume differences between Day 1 and Day 8.

	Group VII	Group VIII	Group IX
Group VII	-	-	-
Group VIII	<i>0.0519</i>	-	-
Group IX	0.0022	0.0043	-
Group X	0.0095	0.0159	0.3524

p values<0.05 in **bold**,<0.06 in *italics*

Table 5: Dose-effect study. Inter-group comparisons of tumor volume medians on Day 8.

mm³ in volume (Figure 2). That was a reduction of nearly 70%. The treatment was well tolerated despite the patient's serious overall health condition. The clinical course of iron oxide and ferritin is shown in Table 6.

Blood samples taken on the fourth treatment day clearly show the specific iron oxide accumulation under the magnet area (Table 7: Sample 2), also demonstrating definitively the carrier function of iron oxide for mitoxantrone. This was 14 times higher than the blood iron level directly before the start of application.

Conclusion

Firstly, the efficiency of the magnetic field as a therapeutic application method is confirmed *in vivo* in both the animal model and the human case study.

Furthermore, the animal study emphasizes the tendency of magnetically mediated chemotherapy to be effective on tumor development with increasing mitoxantrone levels. Even the lowest

dosage applied in the tests reduced tumor growth at borderline significance. On the other hand, the highest drug level administered (Group X, i.e. 8 × 0.5 mg/kg BW) did not significantly raise therapy efficacy.

Regarding the case study no other therapy attempt than a palliative approach is presently reasonable despite general progress in several

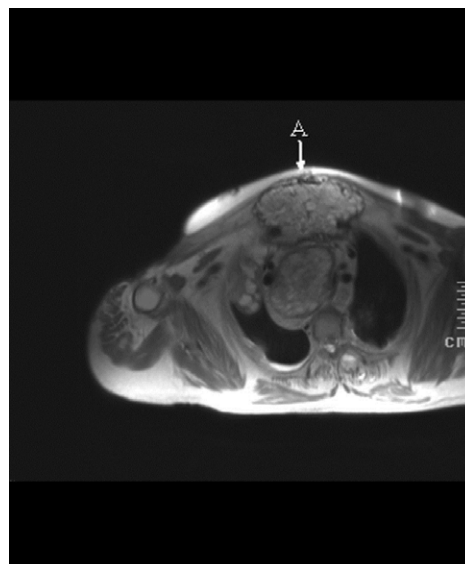


Figure 1: 16/10/2009 coronary MRI layers of thorax T2-dominated, i.e. pre(retro)sternal metastasis (below arrow), prior to therapy (starting 19/10/2009). Metastasis size 635375 mm³.

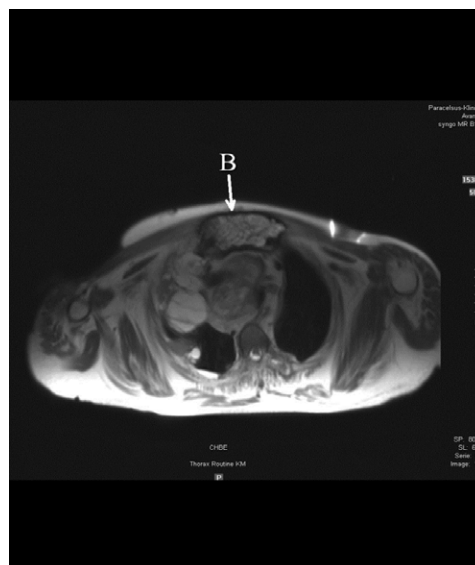


Figure 2: 11/11/2009 pre(retro)sternal metastasis, drastically reduced after therapy, encompassing 196308 mm³.

Patient J.W.	Unit	Day -2	Day 0	Day 1	Day 2	Day 3	Day 4	After 2 weeks
Iron	µg/dl	51	50	64	44	77	136	40
Ferritin	ng/ml	100	755	822	939	968	1290	935

Table 6: Case study. Iron oxide and ferritin on days -2, 0, 1, 2, 3 and 4 and after 2 weeks.

Sample designation		Sample 1	Sample 2
Matrix		blood	tumor tissue under the magnet
Parameter	Unit	content	Content
Microwave pressure break-down HNO ₃ /H ₂ O ₂		X	X
Iron, tot. [Fe]	µg/dl	136	315

Table 7: Case study. Blood sampling on Day 4.

oncological sections. Taking this into account the described remarkable local metastasis reduction by means of magnetic drug targeting indicates an encouraging non-conventional medical alternative to limit metastasis growth. Moreover, although involving a critical stage, noteworthy side effects such as hair loss, stomatitis, gastroenteritis or other clinical symptoms did not occur. This strongly suggests the

usefulness of magnet-assisted therapy approaches, even in severe and palliative disease stages.

References

1. Krukemeyer MG, Wagner W, Jakobs M, Krenn V (2009) Tumor regression by means of magnetic drug targeting. *Nanomedicine* 8: 875-882.
2. Schwerdt JI, Goya GF, Calatayud P, Hereñú CB, Reggiani PC, et al. (2012) Magnetic field-assisted gene delivery: achievements and therapeutic potential. *Curr Gene Ther* 12: 116-126.
3. Petryk AA, Guistini AJ, Gottesman RE, Kaufman PA, Hoopes PJ (2013) Magnetic nanoparticle hyperthermia enhancement of cisplatin chemotherapy cancer treatment. *Int J Hyperthermia* 8: 845-851.
4. Krukemeyer MG, Wagner W (2013) *Nanomedicine in cancer treatment*. J Nanomed Nanotechnol 2: 166.

Citation: Krukemeyer MG, Krenn V, Wagner W, Resch R (2015) Magnetic-mediated Mitoxantrone in Cancer Treatment: *In Vivo* Dosage and Application in a Critical Case. J Nanomed Nanotechnol 6: 330. doi:10.4172/2157-7439.1000330

Submit your next manuscript and get advantages of OMICS Group submissions

Unique features:

- User friendly/feasible website-translation of your paper to 50 world's leading languages
- Audio Version of published paper
- Digital articles to share and explore

Special features:

- 400 Open Access Journals
- 30,000 editorial team
- 21 days rapid review process
- Quality and quick editorial, review and publication processing
- Indexing at PubMed (partial), Scopus, EBSCO, Index Copernicus and Google Scholar etc
- Sharing Option: Social Networking Enabled
- Authors, Reviewers and Editors rewarded with online Scientific Credits
- Better discount for your subsequent articles

Submit your manuscript at: www.editorialmanager.com/biochem