Angiosarcomen: Welke drugs effectief?

Samenvatting

Dit document geeft de resultaten van literatuur onderzoek naar effectieve medicijnen bij angiosarcomen. Bekeken zijn publicaties over de periode ~1999 - ~2005.

Resultaten:

In volgorde van gunstig effect kunnen resultaten worden bereikt met:

1. (recombinant) InterLeukine-2 (rIL-2), lokaal (in de tumor) geïnjecteerd.
   Eventueel in lage dosis aanvullend op radiotherapie.
   Intra-tumorale toediening blijkt effectiever dan peri-tumoraal
   (systemisch is slechter; veel bijwerking en weinig resultaat).
   Bij meer tumoren heeft intra-tumoraal in één tumor ook gunstig effect op de andere tumoren (Onderzoeken Universiteit Utrecht(NL), Sofia en Japanse cases studies)
2. Docetaxel
3. Gemcitabine gevolgd door Docetaxel (in een case waar InterLeukine-2 niet werkte)
4. Doxorubicin / Paclitaxel. Paclitaxel alleen als de angiosarcoom boven de schouderlijn zit (onderzoek Sloan instituut, NY)
   Gunstige effecten van Doxorubicin, voor zover al optredend, zijn zeer beperkt.

Daarbij zij opgemerkt dat:

- rIL-2 ingespoten in de tumor gunstig afsteekt ten opzichte van de overige middelen. Bij rIL-2 is een angiosarcoom case beschreven waarbij patiënt > 2jaar tumorvrij bleef. Verder blijkt bij onderzoek dat rIL-2 bij niet verwijderbare angiosarcomen de ontwikkeling (van metastases) onderdrukte (18 patiënten, hetgeen een grote populatie is gezien de zeldzaamheid)
- Van de "chemo's" levert Docetaxel (in combinatie met bv. Gemcitabine) betere resultaten dan Doxorubicine, Ifosfamide, Antrhracycline. Combinaties met Pioglitazone e.d. lijken ook iets betere resultaten te kunnen leveren.

'Interferon(-alpha1,8)' lijkt enigszins belovend. Echter nog weinig ervaring.

(onderzoeks)publicaties bekeken:

Mede omdat angiosarcomen zo zeldzaam zijn (in NL een paar per jaar. In USA ~60/jaar) worden er weinig onderzoeken en case studies gepubliceerd:

1 Enige onderzoeken:
- 1.1 Retrospectief; drie onderzoeken (121, 161 en 82 patiënten) over 14-26 jaar (2005/2007)
- 1.2 18 patiënten met angiosarcomen. Japan (2002)
- 1.3 20 patiënten met angiosarcomen aan de schedel. Japan (2005)
- 1.4 9 patiënten met angiosarcomen (New York, USA; 1999)

2 Case study's bij angiosarcomen: (opm: groot deel van de publicaties uit Japan

3 Cases study's van drug therapie met onduidelijke dan wel niet-succesvolle resultaten

4 Overige literatuur.

Opmerkelijk is dat veel publicaties van successen van Japanse universiteiten afkomstig zijn die lokaal (in tumor) ingegeven rIL-2, vaak samen met radiotherapie en/of 'chemo' gebruiken (dat is ook volgens onderzoek universiteit Utrecht het effectiefst).

Blijkens eeen studie activeert rIL-2 vooral Lymphokine-activated killer (LAK) cellen. Eerder is aangetoond dat angiosarcoma cellen gevoelig zijn voor LAK-cellen en dat LAK-cellen die 'induced' zijn door rIL-2, de tumorgroei onderdrukken.

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Algemeen:

Mede vanwege de zeldzaamheid van angiosarcomen, zijn er weinig publicaties over Angiosarcomen en geen studies met grote aantallen patiënten.

1 Resultaten met InterLeukine-2

Opm:

- Uit de publicaties blijkt dat dit relatief nieuwe medicijn, ingespoten in de tumor in combinatie met radiotherapie, bij angiosarcomen de meeste kans op "succes" biedt. Waarbij "succes" dan vooral levensduurverlenging met weinig bijverschijnselen (minder "chemo's " zoals Doxorubicine) is. De kans op genezing (>3jaar ziektevrij) is dan nog steeds zeer beperkt. Echter bij 'chemo's' zijn die kansen nog kleiner.
- Naast vooral Japanse universiteiten/klinieken is ook de universiteit Utrecht bij een drietal onderzoeken/publicaties betrokken.

1.1 Case report + onderzoek referentie

Succesvolle behandeling angiosarcoom in de longen.
Kojima etal in Chest. 2003 Dec;124(6):2397-400.
Comment in: Chest. 2004 Jul;126(1):317-8; author reply 318.

Kojima etal rapporteren succesvolle behandeling van een angiosarcoom in de longen middels een combinatie van bestraling en recombinant interleukine-2 (rIL-2).

Verder refereren ze aan het onderzoek van Sasaki etal (2002) bij 18 angisarcoma patiënten, dat liet zien dat hoge doses rIL-2 *(mijn schatting:~0,4-1 miljoen IU/dag?)* de ontwikkeling van metastases onderdrukte en overleving verlengde. Ook noemen ze dat Paclitaxel gunstig kan werken (apoptotic en antiangiogenc).

In de discussie naar aanleiding van dit artikel merken Duck etal van universiteit Leuven o.a. op dat gunstig effect van rIL-2 alleen, zonder radiotherapie, niet is aangetoond. En dat rIL-2 in hoge doses ook bijverschijnselen heeft. Verder dat Paclitaxel ook gunstige effect heeft (hadden Koijama etal zelf ook al aangegeven).

Koijma etal geven in hun response aan dat dat klopt, echter dat hun patiënt nu na twee jaar nog gezond is, wat zeer uitzonderlijk is. En dat de bijverschijnselen bij dit soort biologische drugs van andere, minder ernstige, aard zijn dan bij chemische drugs (hun patiënt had er nauwelijks last van).

Abstract:

Successful treatment of primary pulmonary angiosarcoma.

Kojima K, Okamoto I, Ushijima S, Yoshinaga T, Kitaoka M, Suga M, Sasaki Y., etal.

Department of Respiratory Medicine, Graduate School of Medical Science, Kumamoto University, 1-1-1 Honjo, Kumamoto 860-0811, Japan.

Angiosarcoma in the lung is an uncommon disorder and is usually attributable to metastasis from a primary site. Primary pulmonary angiosarcoma is extremely rare, and the prognosis of affected individuals is dismal, with most patients dying within months of presentation. Indeed, there have been no reported instances of successful treatment of this condition. We now report the case of a patient with primary pulmonary angiosarcoma who responded to a combination of radiotherapy and immunotherapy with recombinant interleukin-2. The patient remains well without signs of recurrence 1 year after initial presentation. This combination therapy may be a promising strategy to prolong the survival of patients with primary pulmonary angiosarcoma.

PMID: 14665530 [PubMed - indexed for MEDLINE]

Uittreksel uit de discussie paragraaf van hun artikel:

Intratumoral injection of rIL-2 also has been shown to be effective for angiosarcoma of the skin.[13] Furthermore, the systemic administration of high doses of rIL-2 was also effective and induced the regression of pulmonary metastasis *(in muizen).*[13] The therapeutic effect of rIL-2 is thought to result both from a direct action on tumor cells and from the activation of natural killer cells and lymphokine-activated killer cells.[14]

Sasaki et al(15 zie ook hfdst 1.2 in dit document) showed that high-dose rIL-2 treatment suppressed the development of distant metastases and prolonged survival in a study of 18 patients with angiosarcoma who did not have such metastases at the beginning of therapy and had not undergone surgical resection. On the basis of these various observations, we treated our patient with a combination of radiotherapy and systemic administration of rIL-2. The treatment yielded an immediate positive response, resulting in almost complete regression of the tumor. Thus, this is the first reported case of the successful treatment of primary pulmonary angiosarcoma. Although further experience is required, we suggest that this concomitant bimodal treatment might be effective in other patients with primary pulmonary angiosarcoma.

Paclitaxel, which exerts antiangiogenic and apoptotic effects, has been shown[16] to possess substantial activity against angiosarcoma as a single agent, even in patients who have been treated previously with radiotherapy or chemotherapy.

Referenties:

13. Masuzawa, M, Mochida, N, Amano, T, et al Evaluation of recombinant interleukin-2 immunotherapy for human hemangiosarcoma in a SCID mice model (WB-SCID). *J Dermatol Sci* **2001;27**,88-94[CrossRef][ISI][Medline]
14. Ihda, H, Tokura, Y, Fushimi, M, et al Malignant hemangioendothelioma. *Int J Dermatol* **1995;34**,811-816[ISI][Medline]
15. Sasaki, R, Soejima, T, Kishi, K, et al Angiosarcoma treated with radiotherapy: impact of tumor type and size on outcome. *Int J Radiat Oncol Biol Phys* **2002;52**,1032-1040[ISI][Medline]
    Zij concluderen in hun abstract:
    CONCLUSION: Radiotherapy, combined with complete resection or adjuvant rIL-2 immunotherapy, could be a promising treatment strategy, leading to prolonged survival in patients with angiosarcoma.
16. Fata, F, O'Reilly, E, Ilson, D, et al Paclitaxel in the treatment of patients with angiosarcoma of the scalp or face. *Cancer* **1999;86**,2034-2037

1.2 Japans onderzoek over 13 jaar met totaal 30 patiënten

Angiosarcoma treated with radiotherapy: impact of tumor type and size on outcome

Int. Journal of Radiation OncologyBiologyPhysics, 2002 Mar 15;52(4):1032-40

R.Sasaki, T.Soejima, K.Kishi, Y.Imajo, S.Hirota, N.Kamikonya, M.Murakami, T.Kawabe, etal
Divisions of Radiology, Kobe University School of Medicine, Hyogo, Japan.

Abstract:

PURPOSE: Angiosarcoma is a rare and highly malignant vascular neoplasm. The purpose of this study was to elucidate the tumor characteristics and evaluate the efficacy of radiotherapy (RT) for angiosarcoma.

MATERIALS AND METHODS: Thirty patients with angiosarcoma (20 males and 10 females, age range 4-89 years, median 66) who received RT from 1986 to 1999 were enrolled in the study. Twenty-four patients had angiosarcoma of the face and scalp (AFS), and 6 patients had angiosarcomas at other sites. AFS was classified into two categories (according to the macroscopic features): nodular AFS (14 patients) and endophytic AFS (10 patients). The median prescribed irradiation dose was 68 Gy. Surgery had been previously performed in 9 patients, and adjuvant immunotherapy using recombinant interleukin-2 (rIL-2) was combined during and after RT in 20 patients. Univariate analyses and calculation of survival by Kaplan-Meier methods were performed.

RESULTS: Local tumor control was obtained in 17 patients (57%). However, 7 (47%) of them developed distant metastases. The median survival time for all patients was 8 months

(7 months for AFS), and the 13-year overall survival rate was 25% (20% for AFS). Twenty-one patients died of angiosarcoma, with the cause of death local failure in 7 patients, distant failure in 7, and both in 7. Tumor type and size were found to be significant prognostic factors (p = 0.004 and p = 0.007, respectively), and age, total amount of rIL-2, gender, radiation dose, and surgery were not. Six patients (4 with nodular AFS and 2 with angiosarcoma in other parts) survived >2 years. No patient with endophytic AFS survived >2 years. Ten patients (33%) died of respiratory failure secondary to pulmonary metastases. High-dose rIL-2 administration suppressed the occurrence of distant metastases (p = 0.006). Two patients developed radiation dermatitis (Radiation Therapy Oncology Group Grade 4).

CONCLUSION: RT, combined with complete resection or adjuvant rIL-2 immunotherapy, could be a promising treatment strategy, leading to prolonged survival in patients with angiosarcoma.

1.3 Onderzoek schedel angiosarcoma bij 20 patiënten

Angiosarcoma of the scalp treated with curative radiotherapy plus recombinant interleukin-2 immunotherapy.

Int J Radiat Oncol Biol Phys. 2005 Apr 1;61(5):1446-53.

Ohguri T, Imada H, Nomoto S, Yahara K, etal

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PURPOSE: To evaluate the effectiveness of curative radiotherapy (RT) plus recombinant interleukin-2 (rIL-2) immunotherapy regarding the treatment results for angiosarcoma of the scalp. Curative resection of angiosarcoma of the scalp is usually difficult because of the diffuse, clinically undetectable local spread. RT is a rational therapeutic approach, because a wide region of the dermis can be treated, while sparing the underlying normal tissues. Recently, the effectiveness of immunotherapy with rIL-2 has also been reported in the treatment of angiosarcoma of the scalp.

METHODS AND MATERIALS: The data of 20 patients with angiosarcoma of the scalp treated with curative RT plus rIL-2 immunotherapy between January 1988 and June 2002 were retrospectively analyzed. The total radiation dose was 70.3 +/- 6.9 Gy. The fractions were 2-3 Gy daily, given 5 d/wk. rIL-2 immunotherapy was performed by transcatheter arterial administration in 10 patients, systemic administration in 11 during the course of RT, and intratumoral injection in 10 during and/or after RT; 12 patients received a combination of two. Five patients underwent limited surgery, and concomitant pacilitaxel chemotherapy was also used in 2 patients.

RESULTS: The median survival time for overall, local recurrence-free, and distant metastasis-free survival was 36.2, 11.1, and 17.8 months, respectively. Local recurrence developed in 7 patients (35%), 4 of whom also had evidence of distant metastases. An additional 7 patients (35%) developed distant metastases alone. Recurrence within the radiation field was recognized in 2 patients with systemic rIL-2 administration alone ($p < 0.05$).

Arterial or intratumoral administration combined with systemic administration of rIL-2 resulted in better distant metaststasis-free survival rates ($p < 0.05$).

CONCLUSION: Curative RT plus rIL-2 immunotherapy provided an efficient, effective means of treating angiosarcoma of the scalp. Arterial or intratumoral administration combined with systemic administration of rIL-2 may prolong survival.

PMID: 15817349 [PubMed - indexed for MEDLINE]

1.4 Lokale toediening IL-2 in combinatie met o.a. bestraling

De therapeutisch resultaten van radiotherapie worden significant verbeterd door gelijktijdige inzet van lokaal toegepaste Interleukine-2 bij agressieve (infiltrative) tumoren met uitzaaiingen.

Treatment of stage III–IV nasopharyngeal carcinomas by external beam irradiation and local low doses of IL-2

Cancer Immunology, Immunotherapy, 2005, vol. 54, no8, pp. 792-798 [7 pages; 29 ref.]

John J. L. Jacobs[1], Gerrit J. Hordijk[2], Ina M. Jürgenliemk-Schulz[3], Chris H. J. Terhaard[3], Jan W. Koten[1], Jan J. Battermann[3] and Willem Den Otter[1]

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Abstract

The therapeutic effect of intratumoural application of Interleukin-2 (IL-2) was studied in patients with stage III–IV nasopharyngeal carcinoma (NPC) that received radiotherapy. Patients with stage III–IV NPC receiving a standard treatment of 7,000 cGy external beam irradiation have a mean disease-free survival of about 1.5 years.

In this paper, we describe ten of these patients who were treated with additional peritumoural and intratumoural injections with 3x10 U IL-2 on 5 days in weeks 2, 4, and 6 of the 7-weeks' irradiation period. This combined treatment group was compared with a historical group of patients treated with standard irradiation alone.

Local IL-2 therapy showed a marked clinical and statistical significant improvement of disease-free survival. After 5 years, 63% of the IL-2 treated patients were disease-free versus 8% of the control patients.

These results suggest that the therapeutic results of radiotherapy can be significantly improved by combining it with local IL-2 treatment. To our knowledge, this is the first clinical report showing that local IL-2 therapy is effective against an infiltrative and locally metastasizing tumour in human patients.

Study also presented at Dutch Society for Immunology, Dec. 2003, Noordwijkerhout, NL

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1.5 Lokale Interleukine-2 (RiL-2) bij darm kankers, incl. 1 angiosarcoom

Releatief gunstige resultaten en geringe bijwerking bij ‘hopeloze’ kankerpatiënten mede dankzij lokale/regonale toediening.
Onderzoek universiteit hospitaal Sofia, Bulgarije. Medeauteurs: Jan-Willem Koten, John Jacobs, Professor Willem den Otter zijn van afd. Pathobiology, Universiteit Utrecht).

Locoregional IL-2 low dose applications for gastrointestinal tumors.

World J Gastroenterol. 2005 Sep 21; 11(35) : 5525-9.

Krastev Z, Koltchakov V, Tomova R, Deredjian S, Alexiev A, Popov D, Tomov B, Jan-Willem Koten, John Jacobs, Willem den Otter.

AIM: To explore the feasibility of local interleukin 2 (IL-2) in patients with different forms of abdominal cancer. This required experimentation with the time interval between IL-2 applications and the methods of application.

METHODS: Sixteen patients with stages III and IV of gastrointestinal malignancies (primary or metastatic) who were admitted to our Department of Gastroenterology were treated with locoregionally applied IL-2 in low doses.

RESULTS: No major problems applying locoregional IL-2 were encountered. In 6 out of 16 patients, a modest but clinically worthwhile improvement was obtained. These patients suffered from colorectal carcinoma, hemangiosarcoma or hepatocellular carcinoma with liver fibrosi. Adverse effects were minimal. The therapeutic scheme was well tolerated, even in patients in a poor condition.

CONCLUSION: This study demonstrates the feasibility of low dose locoregional IL-2 application in advanced abdominal cancer. Local IL-2 therapy gives only negligible adverse effects. The results suggest that it is important to apply intratumorally. Local IL-2 may be

given adjunct to standard therapeutic regimes and does not imply complex surgical interventions. These initial results are encouraging.

The one patiënt with (hem)angiosarcoma in this study had a life expectancy of less than 3 months. He had marked improvement in general condition and lived for 12 months.
(zie ook: http://www.geocities.com/cancerimmunotherapy/human7.html)

1.6 Intra-tumorale toediening Interleukine-2 effectiever

Bij onderzoek op muizen van universiteit Utrecht, blijkt dat:
- intra-tumorale toediening effectiever is dan peri-tumorale (en zeker dan systemische)
- inspuiting van de IL-2 bij muizen met twee tumors, in alleen één van de twee tumors ook tot gevolg heeft dat de andere tumor in omvang afneemt (wel minder sterk)!

=> Ze bevelen direct inspuiting in de tumor aan.

Local interleukin 2 therapy is most effective against cancer when injected intratumourally.

Cancer Immunol Immunother. 2005 Jul;54(7):647-54. Epub 2005 Feb 1.

Jacobs JJ, Sparendam D, Den Otter W.

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Local interleukin 2 (IL-2) therapy is more effective against systemic tumours than systemic IL-2 therapy, but it remains unclear whether IL-2 should be injected intratumourally or peritumourally. To investigate this question, we treated DBA/2 mice bearing a large subcutaneous syngeneic SL2 lymphoma with either intra or peritumoural IL-2 therapy.

Both applications enhanced survival, but intratumourally injected IL-2 was more effective than peritumourally injected IL-2. Tumours started to regress 4 days after IL-2 injection. Tumour cells died at the IL-2 injection site, although IL-2 is not directly cytotoxic for SL2 cells in vitro. Tumour cell death correlated well with oedema and extravascular erythrocytes, but less with leukocyte infiltrates. In mice bearing two s.c. tumours, intratumoural application therapy of IL-2 in one tumour caused decrease in size of both tumours in 4-9 days after therapy. However, the IL-2 treated tumours regressed more strongly than the untreated tumours. We conclude that vascular leakage and/or tissue destruction inside the tumour may contribute to the enhanced effect of intratumoural IL-2 therapy compared to peritumoural IL-2 therapy.
Hence, we recommend applying of intratumoural rather than peritumoural IL-2 therapy.

Zie elders in dit document voor de (naar verhouding) goede klinische resultaten van Japanse universiteiten met lokaal toegediende InterLeukine-2.

1.7 recombinant InterLeukin-2 (rIL-2) in combinatie met …

Bestraling en chemo.

1.7.1 2001, vagina, Fukiushima Medical University

Combinatie rIL-2 met chemotherapie heeft (een jaar) gewerkt:

Angiosarcoma of vagina successfully treated with interleukin-2 therapy and chemotherapy: a case report.

J Obstet Gynaecol Res. 2001 Aug;27(4):231-5.

Morimura Y, etal

Department of Obstetrics and Gynecology, Fukiushima Medical University, Japan.

We report a case of angiosarcoma of the vagina in a 61-year-old woman who had undergone radical hysterectomy and pelvic irradiation for uterine cervical adenocarcinoma 14 years

previously. Combination chemotherapy (cyclophosphamide, vincristine, doxorubicin and dacarbazine) and interleukin-2 induced complete remission of the tumor.

The patient remained free from disease for 15 months.

PMID: 11721736 [PubMed - indexed for MEDLINE]

1.7.2 Combinatie met rIL-2 met o.a. interferon alpha-2b

Successful treatment of angiosarcoma of the scalp by intralesional cytokine therapy and surface irradiation.

J Eur Acad Dermatol Venereol. 2000 Sep;14(5):412-5.

Comment in: J Eur Acad Dermatol Venereol. 2001 Jul;15(4):370-1.

Ulrich L, Krause M, Brachmann A, Franke I, Gollnick H.

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An 88-year-old woman presented to us with angiosarcoma of the scalp that had developed over a 6-month period following previous trauma. Despite explicit information concerning the extremely malignant potential of the tumour the patient refused any surgical intervention. However, she agreed to receive local, intralesional interferon alpha-2b and interleukin-2 therapy. After partial remission of the tumour, the intralesional cytokine injections were combined with surface radiotherapy. This combination therapy led to a 2-year remission of both the tumour and sonographically suspicious cervical lymph nodes. Apart from the typical, moderate side-effects of interferon alpha-2b and interleukin-2 the therapy was well tolerated. In conclusion, in our limited experience intralesional cytokine therapy--alone as well as in combination with surface irradiation--seems to be an alternative therapeutic option for patients who is not a candidate for surgery.

PMID: 11305388 [PubMed - indexed for MEDLINE]

1.7.3 2005; interleukine met chemo en bestraling

Complete remission in a patient with angiosarcoma by the combination of OK-432, rhIL-2, and radiotherapy.

Eur J Dermatol. 2005 Sep-Oct;15(5):411-3.

Inaba T, **Yamanaka K**, etal

Abstract niet (vrij) beschikbaar.

PMID: 16208887 [PubMed - indexed for MEDLINE]

1.8 Case reports met recombinant InterLeukin-2 (rIL-2)

Uit de publicaties blijkt dat dit een van de effectiefste medicijnen is bij angiosarcoma.

Opvallend is dat het praktisch alleen Japanse publicaties zijn (in redelijk vooraanstaande engelstalige wetenschappelijke tijdschriften).

1.8.1 2005, vagina, Kobe university

A case of postirradiation vaginal angiosarcoma treated with recombinant interleukin-2 therapy.

Int J Gynecol Cancer. 2005 Nov-Dec;15(6):1163-5.

Takeuchi K, etal

Dept of Obstetrics and Gynecology, Kobe University, Japan. kyousuket@dolphin.ocn.ne.jp

Angiosarcoma of the vagina is an extremely rare neoplasm and is characterized by frequent recurrence and early metastatic spread. Although previous reports emphasized the poor prognosis of this disease, effective treatment strategies have not been adequately stated. We report a case of angiosarcoma of the vagina, in which the diagnosis was made 9 years after

intrapelvic irradiation, and recombinant interleukin-2 (rIL-2) therapy could be effective to suppress the development of distant metastasis.

We recommend rIL-2 therapy in combination with irradiation as a palliative therapeutic option for vaginal angiosarcoma when the tumor is inoperable or the patient refuses to undergo surgery. …..

PMID: 16343203 [PubMed - indexed for MEDLINE]

1.8.2 2006, neus, Kyoto Second Red Cross Hospital

A case of angiosarcoma of the nasal cavity successfully treated with recombinant interleukin-2.

Otolaryngol Head Neck Surg. 2006 May;134(5):886-7.

Fukushima K, Dejima K, Koike S, Tei G, Asano J, Ueda M, Hyuga M, Oshima W.

Department of Otolaryngology, Kyoto Second Red Cross Hospital, Kyoto, Japan.

Geval van 55 jaar oude man die operatie weigerde. Daarop werden hem intravenous injecties met rIL-2 gegeven met een dosis van 400.000 u/dag gedurende 6 dagen. De tumor werd toen 50% kleiner. Mede vanwege de neveneffecten van de rIL-2 stemde de man alsnog toe in operatie, waarbij de tumor werd verwijderd. Postoperatief werd radiotherapie toegepast (totale dosis 50 Gy). Na drie jaar is hij nog steeds tumorvrij.

Artikel bij mij beschikbaar (geen abstract in PubMed).

1.8.3 2006, ooglid, Kansai Rosai Hospital, Amagasaki

Treatment of eyelid lesion of angiosarcoma with facial artery recombinant interleukin-2 (rIL-2) injection.

J Am Acad Dermatol. 2006 May;54(5):907-8.

Miura H, en Asada Y.

Een 92 jaar oude man. Arteriële injecties met rIL-2 werden gerealiseerd door eenmalig een katheder in de betrokken gezicht-slagader (katheder aangebracht onder verdoving) aan te brengen. Dankzij de katheder behoefde de patiënt niet in het hospitaal te worden opgenomen Deze injecties met een dosis van 700.000 IU/dag, leverden na 3 weken zeer sterke reductie van de tumor.

PMID: 16635681 [PubMed - indexed for MEDLINE]

2 Resultaten met Docetaxel

2.1 Docetaxel bij bestrijding long metastase (Japan, 2x)

Successful treatment of pulmonary metastasis and local recurrence of angiosarcoma with docetaxel.

J Dermatol. 2004 Apr;31(4):335-41.

Isogai R, Kawada A, Aragane Y, Tezuka T.

Dept of Dermatology, Kinki University School of Medicine, Osaka-Sakayama City, Osaka, Japan.

Angiosarcoma of the face and scalp of the elderly frequently recurs locally, metastasizes early despite various treatments, and has a poor prognosis. We describe a patient who had angiosarcoma of the scalp with pulmonary metastasis. Local recurrence occurred after excision and local and arterial administration of IL-2. A weekly administration method of docetaxel was therefore selected, resulting in complete remission of the pulmonary metastasis and a partial response of the local recurrence. This favorable clinical outcome in our case suggests that docetaxel therapy may be an option for the treatment of angiosarcoma of the scalp with pulmonary metastasis.

PMID: 15187330

Weekly low-dose docetaxel in the treatment of lung metastases from angiosarcoma of the head.

Br J Dermatol. 2005 Apr;152(4):811-2. Links

Yamada M, Hatta N, Mizuno M, Oishi N, Takehara K.

Abstract niet vrij beschikbaar.

PMID: 15840125

2.2 Oncology Centre Glasgow, 2006, borst angiosarcoom

Radiation-induced angiosarcoma of the breast shows major response to docetaxel after failure of anthracycline-based chemotherapy.

Breast. 2006 Feb;15(1):117-8. Epub 2004 Dec 25.

Mano MS, etal

Beatson Oncology Centre, Western Infirmary, Dumbarton Road, Glasgow, UK. max.mano@northglasgow.scot.nhs.uk

We report on the case of a patient with a diagnosis of an uncommon breast tumour, namely a radiation-induced angiosarcoma, which was primarily refractory to anthracycline-based chemotherapy, but highly sensitive to docetaxel. Although the sarcomas in general tend to be relatively refractory to taxanes, there is some evidence that the angiosarcomas may be sensitive to these agents. This is particularly well documented with paclitaxel, but may also be the case with docetaxel.

PMID: 16473744 [PubMed - indexed for MEDLINE]

2.3 Combinatie docetaxel, doxorubin en ifosfamide? (Cleveland)

Resultaten niet om enthousiast van te worden.

Phase I/II study of docetaxel, ifosfamide, and doxorubicin in advanced, recurrent, or metastatic soft tissue sarcoma (STS).

Invest New Drugs. 2006 Jun 21

Suppiah R, etal

Department of Hematology and Medical Oncology, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Desk R35, Cleveland, Ohio, 44195, suppiar@ccf.org.

Background: Based on reports of the efficacy of docetaxel (T) in STS, we undertook a phase I/II trial to determine the response rate (RR), dose-limiting toxicity (DLT), and maximum tolerated dose (MTD) of addition of T to doxorubicin (A) and ifosfamide (I) in advanced STS.

Methods: Patients with advanced, recurrent, or metastatic STS, without prior chemotherapy, were enrolled in a dose escalation trial. Dose levels: I-A 40 mg/m(2); I 4.0 gm/m(2); T 40 mg/m(2), II-A 50; I 5.0; T 50, III-A 60; I 6.0; T 60, and IV-A 75; I 7.5; T 75. MTD was defined as the dose producing DLTs in >/=2 of 3-6 patients treated.

Results: 21 patients were accrued. Median age: 55 (28-78) years. Histology: leiomyosarcoma 10, spindle cell sarcoma 3, synovial sarcoma 2, angiosarcoma 1, fibrous histiocytoma 1, epitheliod hemangio-endothelioma 1, and 3 not specified. MTD was level III (A 60, I 6.0, and T 60). DLT was myelosuppression. All grade 4 toxicities were hematologic. Patients received median 2 cycles (range 2-9).

Eight patients (38%) achieved partial response (PR). PR occurred after six cycles in 5 patients. 18 patients died. Median overall survival: 17 months (95% CI, 9.1-33.6 months).

Conclusions: The recommended Phase II dose of this combination is level III: A 60 mg/m(2), I 6.0 g/m(2), T 60 mg/m(2), with mesna and granulocyte-colony stimulating factor. The RR is similar to that of AI in other trials, but the survival is better than anticipated.

PMID: 16791410 [PubMed - as supplied by publisher]

2.4 Onderzoek 35 patiënten met diverse sarcomen (incl angiosarcoom)

Combinatie Gemcitabine gevolgd door Doccetaxel lijkt effectief.

Laboratory and clinical evidence of synergistic cytotoxicity of sequential treatment with gemcitabine followed by docetaxel in the treatment of sarcoma

J Clin Oncol. 2004 May 1;22(9):1706-12 (uit PubMed)

Leu KM, Ostruszka LJ, Shewach D, Zalupski M, Sondak V, etal

Department of Medicine, Division of Hematology/Oncology, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI 48109, USA.

PURPOSE: A recent report of the combination of gemcitabine and docetaxel described favorable results in patients with uterine leiomyosarcoma. The objective of this report is to describe experience with this combination in a variety of histologic subtypes of sarcoma. Additionally, cell-culture studies were performed to assess the effect of the sequence of drug administration on colony formation.

PATIENTS AND METHODS: A medical record review of 35 patients receiving the gemcitabine/docetaxel combination was undertaken. Gemcitabine 675 mg/m(2) intravenously was administered over 90 minutes on days 1 and 8, and docetaxel 100 mg/m(2) intravenously was administered over 60 minutes on day 8 of a 21-day cycle. Cell culture studies using the SAOS-2 osteosarcoma cell line and MCF-7 breast cancer cell line were also performed. Gemcitabine and docetaxel were added to cells either simultaneously for 24 hours, gemcitabine for 24 hours followed by docetaxel for 24 hours, or the reverse sequence.

RESULTS: Thirty-five patients were treated. Five complete responses and 10 partial responses were observed for an overall response rate of 43%.

Responses occurred in uterine, extremity, and retroperitoneal leiomyosarcoma, osteosarcomas, angiosarcomas, malignant fibrous histiocytomas, malignant peripheral-nerve sheath tumors, and Ewing's sarcoma.

In the cell culture studies, gemcitabine followed by docetaxel provided synergy. In contrast, the administration of drugs simultaneously resulted in antagonism, and docetaxel followed by gemcitabine provided mixed results.

CONCLUSION: The combination of gemcitabine and docetaxel seems to be active in a variety of sarcomas. A multicenter, randomized clinical trial in soft tissue sarcoma comparing gemcitabine alone with this combination, is ongoing.

PMID: 15117993

2.5 Doctaxel; relatief goed bij angiosarcomen op of nabij de huid

Docetaxel: a therapeutic option in the treatment of cutaneous angiosarcoma: report of 9 patients.

Cancer. 2007 Aug 1;110(3):648-51
Nagano T, **Yamada Y**, **Ikeda T**, **Kanki H**, **Kamo T**, **Nishigori C**.

Division of Dermatology, Department of Clinical Molecular Medicine, Kobe University Graduate School of Medicine, Kobe, Japan. nagano@med.kobe-u.ac.jp

BACKGROUND: Effective treatment options are limited for patients with cutaneous angiosarcoma (AS). Docetaxel, a member of the taxane family of drugs, reportedly has been effective in the treatment of lung, head and neck, and breast cancers. Another taxane drug, paclitaxel, reportedly had unique activity in the treatment of AS of the scalp and neck and acquired immunodeficiency syndrome-related Kaposi sarcoma. Therefore, the authors hypothesized that docetaxel may be of value in the treatment of cutaneous AS that is resistant to conventional therapy. However, there were only 3 case reports of the successful treatment of AS in elderly patients using docetaxel in combination with surgery and radiotherapy.

METHODS: This was a retrospective trial. After written informed consent was obtained, docetaxel was administered intravenously at a dose of 25 mg/m(2) for 1 hour weekly over a period of 8 weeks on the basis of previous reports. This treatment regimen was received by 9 patients with cutaneous AS who were treated at Kobe University Hospital between January 2003 and October 2006.

RESULTS: Six of the 9 patients who received treatment achieved major responses, including 2 complete responses and 4 partial responses. Neutropenia and peripheral neuropathy were not prominent, although severe radiation dermatitis enhanced by the docetaxel was observed in 3 patients. There were no deaths attributable to this therapy.

CONCLUSIONS: The current study demonstrated that docetaxel was effective in patients with cutaneous AS. (c) 2007 American Cancer Society.

PMID: 17582627 [PubMed - indexed for MEDLINE]

2.6 Case succesvol behandeld met Docetaxel

Successful treatment of pulmonary metastasis and local recurrence of angiosarcoma with docetaxel.

J Dermatol. 2004 Apr;31(4):335-41.
Isogai R, **Kawada A**, **Aragane Y**, **Tezuka T**.

Department of Dermatology, Kinki University School of Medicine, Osaka-Sakayama City, Osaka, Japan.

Angiosarcoma of the face and scalp of the elderly frequently recurs locally, metastasizes early despite various treatments, and has a poor prognosis. We describe a patient who had angiosarcoma of the scalp with pulmonary metastasis. Local recurrence occurred after excision and local and arterial administration of IL-2. A weekly administration method of docetaxel was therefore selected, resulting in complete remission of the pulmonary metastasis and a partial response of the local recurrence. This favorable clinical outcome in our case suggests that docetaxel therapy may be an option for the treatment of angiosarcoma of the scalp with pulmonary metastasis.

PMID: 15187330 [PubMed - indexed for MEDLINE]

3 Paclitaxel: vooral effectief op/boven schouderlijn

Vooral kans op effectiviteit bij angio-sarcoom op of boven de schouderlijn/sleutelbeen.

3.1 Effect bij 9 patiënten met angiosarcoom in hoofdhuid of gezicht

Paclitaxel in the treatment of patients with angiosarcoma of the scalp or face

Cancer 1999;86:2034-7. © 1999 American Cancer Society.

Farid Fata, Eileen O'Reilly, David Ilson, David Pfister, David Leffel, David P. Kelsen, etal

Gastrointestinal Oncology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center and Cornell University Medical College, New York, New York

Yale University School of Medicine, New Haven, Connecticut

BACKGROUND Angiosarcomas are rare tumors. Based on a complete response observed in a patient with angiosarcoma of the scalp treated with paclitaxel in a Phase II trial, the authors treated a cohort of patients with angiosarcoma of the scalp or face with paclitaxel as single agent.

METHODS The authors identified nine patients with angiosarcoma of the scalp or face treated at Memorial Sloan-Kettering Cancer Center with paclitaxel between January 1992 and December 1998. Various paclitaxel schedules were used over 1, 3, and 24 hours.

RESULTS Of the 9 patients, 8 had major responses (4 partial responses and 4 clinical complete responses) and 1 had a minor response, for a major response rate of 89%. The median duration of response was 5 months (range, 2-13 months). Neutropenia and peripheral neuropathy were the most frequent dose-limiting toxicities. No deaths were attributed to therapy.

CONCLUSIONS Paclitaxel as a single agent has substantial activity against angiosarcoma of the scalp or face, even in patients previously treated with chemotherapy or radiation therapy. Further investigation is warranted to define the optimal treatment dose and schedule.

3.2 Effect bij 32 patiënten

Paclitaxel in patients with advanced angiosarcomas of soft tissue: A retrospective study of the EORTC soft tissue and bone sarcoma group.

Eur J Cancer. 2008 Sep 2. [Epub ahead of print]
Schlemmer M, **Reichardt P**, **Verweij J**, **Hartmann JT**, **Judson I**, **Thyss A**, **Hogendoorn PC**, **Marreaud S**, **Glabbeke MV**, **Blay JY**.

Medical Clinic and Polyclinc III, Clinic Grosshadern Munich, Ludwig-Maximilian-University Munich, Marchioninistrasse 15, D-81377 Muenchen, Germany.

RATIONALE: Angiosarcomas of soft tissue represent a heterogenous group of rare sarcomas with specific clinical behaviour and risk factors. Paclitaxel appears to induce tumour control in a higher proportion of patients with angiosarcoma, as compared to other

sarcomas. The objective of this retrospective study was to assess the anti-tumour activity of this compound in a multicentre setting.

METHOD: Clinical data from patients with angiosarcomas of soft tissue treated with single agent paclitaxel were collected from the centres of the soft tissue and bone sarcoma group of EORTC, using a standardised data collection form. Paclitaxel could be given every three weeks, or weekly. Statistical analysis was performed using SAS software.

RESULTS: Data from 32 patients were collected from 10 centres. There were 17 males, 15 females, with a median age of 60.4 years (range, 25-91). Primary angiosarcomas were located in scalp and face in 8 patients (25%) and at other primary sites in 24 patients (75%). All patients had intermediate (n=13) or high grade (n=19) primary tumours. Thirteen (40%) patients had been pretreated with doxorubicin-based first-line-chemotherapy and three of them (9%) had also received second-line chemotherapy with ifosfamide. Eleven (34%) patients had been irradiated before as treatment for angiosarcoma. In 8 (25%) patients, the angiosarcoma occurred at sites of prior radiation therapy for other malignancies. The response rate was 62% (21/32) in the whole series, 75% (6/8) in scalp angiosarcomas and 58% (14/24) in other primary sites. The median time to progression was 7.6 months (range, 1-42) for the whole group. For the face/scalp group it was 9.5 months, and for patients with angiosarcomas at other sites it was 7.0 months, respectively.

CONCLUSION: Paclitaxel was found to be an active agent in angiosarcoma of soft tissue in this retrospective analysis. These results need to be confirmed in a prospective randomised phase II study.

PMID: 18771914

4 Doxorubicin succesvol bij angiosarcoom aan de hoofdhuid

Complete remission of a radio-resistant cutaneous angiosarcoma of the scalp by systemic treatment with liposomal doxorubicin.

Br J Dermatol. 2002 Jul;147(1):150-3.
Eiling S, **Lischner S**, **Busch JO**, **Rothaupt D**, **Christophers E**, **Hauschild A**.

Department of Dermatology, University of Kiel, Schittenhelmstrasse 7, Germany.

We report an 80-year-old man suffering from an angiosarcoma of the scalp. Because of the wide extent of the lesions, surgery was not performed. Instead, the patient was treated with electron-beam radiation. Later, the patient failed to benefit from radiotherapy demonstrated by a local relapse and new malignant lesions. Additionally, a cervical lymph node metastasis appeared for the first time. Subsequently, we successfully administered liposomal doxorubicin (Caelyx(R)). Shortly after administration of two cycles the scalp angiosarcoma showed a clear regression. Following six cycles, the patient clinically showed a complete remission of all skin lesions and the cervical lymph node; metastasis was confirmed by histology and fine needle aspiration, respectively. Liposomal and pegylated doxorubicin, a cytostatic drug belonging to the anthracyclines, has already shown to be effective and mostly well tolerated in the therapy of acquired immune deficiency syndrome-related Kaposi's sarcoma and very recently in cutaneous T-cell lymphoma, too. Caelyx(R) appears to be a promising alternative to conventional treatment of cutaneous angiosarcoma.

PMID: 12100199

5 Algemene retrospectieve onderzoeken

5.1 Onderzoek Sloan instituut New York 121 patënten

Conclusies retrospectief onderzoek over periode van 14-jaar van het Sloan kanker instituut New York (2005):

Oppervlakkigheid van de tumor (dichter bij de huid blijvend) en ruimere marges rond de tumor bij de operatieve verwijdering, leverden een verhoogde overlevingskans.
Omvang van de tumor was minder belangrijk voor de overlevingskans. De overall 5jaars overlevingskans was ~30%.

Voor angiosarcomen die niet konden worden verwijderd:

- Doet Paclitaxel het alleen goed voor angiosarcomen in schouder/nek/hoofd (stabilisatie tumor gemiddeld 6 maanden).
  Opm: Deze conclusie wordt ook door andere publicaties ondersteund.
- Leverde behandelingen waarbij ook Doxorubicin werd toegepast stabilisatie van de tumor gedurende 3 – 5 maanden

Er wordt geen melding gemaakt van ervaringen met Docetaxel, Gemmcitubine, of rIL-2.

A 14-year retrospective review of angiosarcoma: clinical characteristics, prognostic factors, and treatment outcomes with surgery and chemotherapy

Cancer J. 2005 May-Jun;11(3):241-7. Erratum in: Cancer J. 2005 Jul-Aug;11(4):354.

Fury MG, Antonescu CR, Van Zee KJ, Brennan MF, Maki RG.

Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York, USA.

PURPOSE: Angiosarcoma is a rare vascular malignancy, and there are few published data to guide chemotherapy treatment decisions. We present a retrospective analysis of angiosarcoma encompassing all anatomic sites of disease presenting to a single institution over a 14-year period. Characteristics at presentation and prognostic factors are reviewed. For patients with unresectable disease, progression-free survival with various chemotherapy regimens is described.

PATIENTS AND METHODS: Pathological confirmation of all cases was performed before they were included in this analysis. One hundred twenty-five patients with angiosarcoma were seen and treated between January 1, 1990 and December 31, 2003.

RESULTS: Angiosarcoma showed marked variation by anatomic site regarding gender ratio, median age at diagnosis, overall survival, and response to chemotherapy. Overall 5-year survival was 31% for angiosarcoma. Superficial depth and negative microscopic surgical margins correlated with longer overall survival, but tumor size did not reach significance as a prognostic factor.

For unresectable angiosarcoma, doxorubicin based regimens yielded progression-free survival of 3.7-5.4 months.

Paclitaxel achieved a progression-free survival of 6.8 months for scalp angiosarcoma and 2.8 months for sites below the clavicle.

DISCUSSION: Angiosarcoma is an aggressive malignancy characterized by biologic heterogeneity at different anatomic sites and relative sensitivity to paclitaxel and doxorubicin.

PMID: 16053668 [PubMed - indexed for MEDLINE]

5.2 Onderzoek bij 161 patiënten in Frankrijk

Het onderzoek bestreek alle gevallen in drie ziekenhuizen over een periode van 24jaar.

De prognose verslechterde als de tumor voorkwam:

- in de Lever (RR 12,6)

- op meer plaatsen (RR 3,8)
- uitzaaiïngen
- aanwezigheid in weke delen

Angiosarcomas, a heterogeneous group of sarcomas with specific behavior depending on primary site: a retrospective study of 161 cases.

Ann Oncol. 2007 Dec;18(12):2030-6. Epub 2007 Oct 31.

Fayette J, **Martin E**, **Piperno-Neumann S**, **Le Cesne A**, **Robert C**, **Bonvalot S**, **Ranchère D**, **Pouillart P**, **Coindre JM**, **Blay JY**.

Hospices Civils de Lyon, Université Lyon 1, Hôpital Edouard Herriot, Oncologie Médicale, Pavillon E, Lyon, France. jfayette@9online.fr

BACKGROUND: Angiosarcomas are rare, heterogeneous and a retrospective study was conducted to describe their natural history.

PATIENTS AND METHODS: We reviewed 161 files of angiosarcoma treated in three institutions of the French Sarcoma Group from 1980 to 2004. Survival and prognostic factors for survival were analyzed.

RESULTS: Median age was 52 years. Primary sites were the breast (35%), skin (20%) and soft tissues (13%). At initial diagnosis, 31 (19%) had metastases. Surgery was the first treatment in 121 (75%) patients combined with chemotherapy or radiotherapy in 34 and 32, respectively. Ninety (74%) of these 121 patients relapsed, mostly locally (50).
With an average time since initial diagnosis of 8.1 years, 123 (76%) patients progressed and 76 (47%) died. Median survival was 3.4 years [95% confidence interval (CI) 2.4-5.8], and the 5-year overall survival (OS) rate was 43% (95% CI 33-53).
In multivariate analysis, liver primary site [relative risk (RR) = 12.62], performance status (PS) of two or more (RR = 3.83), presence of metastases at diagnosis (RR = 2.50), soft tissue tumor (RR = 0.31) were correlated to OS. PS, liver and soft tissue tumors were identified as independent prognostic factors for progression-free survival.

CONCLUSIONS: Angiosarcomas have an overall poor outcome, but with a clearly distinct prognosis depending on the primary site.

PMID: 17974557 [PubMed - indexed for MEDLINE]

6 Hormenen & Interferon

Lijkt veelbelovend. Waar rIL-2 klinisch in vooral Japan succesvol wordt gebruikt bij angiosarcoma, moet de klinische toepassing van IFN-alpha1,8 nog van de grond komen.

6.1 Interferon-alpha1,8 effectief? (2006)

IFN-alpha1,8 inhibits tumor-induced angiogenesis in murine angiosarcomas.

J Interferon Cytokine Res. 2006 May;26(5):353-61.

Taylor KL, Oates RK, Grane R, Leaman DW, Borden EC, Lindner DJ.

Cleveland Clinic Foundation, Center for Hematology and Oncology Molecular Therapeutics, Cleveland, OH 44195, USA.

Interferon-alpha (IFN-alpha) has proved effective in the treatment of hemangiomas, hemangioblastomas, and Kaposi's sarcoma. To investigate the ability of IFNs to inhibit angiosarcoma, we used two transformed murine endothelial cell lines that form angiosarcomas in vivo. SVR and MS1-VEGF cell lines express oncogenic H-ras or vascular endothelial growth factor (VEGF), respectively. IFN-alpha1,8, which is active against

murine and human cells, inhibited SVR and MS1-VEGF proliferation in vitro by 40% at 10(3) U/mL (p = 0.028). In vivo, IFN-alpha1,8 inhibited SVR tumor volume by 71% (p = 0.047) and MS1-VEGF volume by 79% (p = 0.003). Tumor-induced angiogenesis was decreased in SVR tumors by 52% (p = 0.005) and in MS1-VEGF tumors by 58% (p = 0.001).

Sera from IFN-alpha1,8-treated mice bearing either SVR or MS1-VEGF tumors demonstrated a 5-fold increase in IP-10/CXCL10 (p = 0.001), an IFN-induced antiangiogenic protein.

Both recombinant IP-10 and IFN-alpha1,8 inhibited human umbilical vein endothelial cell (HUVEC) vessel formation in the fibrin gel assay, a three-dimensional culture model of angiogenesis, by 56% at 25 ng/mL and 50% at 1.2 ng/mL, respectively (p < 0.001). An IP-10 blocking antibody restored vessel formation to 80% of untreated controls (p = 0.001).

Given the magnitude of the in vivo response, these data suggested that the antitumor effects of IFN-alpha1,8 were likely mediated through angiogenesis inhibition rather than solely by direct inhibition of tumor cell proliferation.

6.2 Hormonen; redelijk effectief? (slechts 1 study)

Primary malignant tumors of the heart: four cardiovascular hormones decrease the number and DNA synthesis of human angiosarcoma cells.

Cardiology. 2006;105(4):226-33. Epub 2006 Mar 3.

Vesely BA, etal

Department of Biochemistry and Molecular Biology, University of South Florida Cardiac Hormone Center Tampa, FL 33612, USA.

BACKGROUND: A family of six cardiovascular hormones--atrial natriuretic peptide, brain natriuretic peptide, C-natriuretic peptide, long acting natriuretic peptide, vessel dilator and kaliuretic peptide--was investigated for the ability to decrease the number of human angiosarcoma cells.
METHODS AND RESULTS: Within 24 h, vessel dilator, long acting natriuretic peptide, kaliuretic peptide, atrial natriuretic peptide and their intracellular mediator cyclic GMP decreased the number of angiosarcoma cells by 61, 30, 29, 36 and 32%, respectively, and DNA synthesis by 68-85%. Brain natriuretic peptide and C-natriuretic peptide had no effect(s). The natriuretic peptide receptor C was present.
CONCLUSIONS: Four cardiovascular hormones decrease the number of angiosarcoma cells within 24 h via inhibition of DNA synthesis mediated in part by cyclic GMP.
 (*vergelijkbare related articles gevonden)*

PMID: 16534199 [PubMed - in process]

7 Andere & combinatie medicijnen

7.1 Pioglitazone, rofecoxib, and metronomic trofosfamide

Beter dan ... Maar geen geweldige resultaten.

Antiangiogenetic therapy with pioglitazone, rofecoxib, and metronomic trofosfamide in patients with advanced malignant vascular tumors.

Cancer. 2003 Nov 15;98(10):2251-6.

Vogt T, Hafner C, Bross K, Bataille F, Jauch KW, etal

Dept of Dermatology, University of Regensburg, Germany. thomas.vogt@klinik.uni-regensburg.de

BACKGROUND: Systemic therapy options for patients with advanced angiosarcomas are limited, and their prognosis is poor. The idea of angiostatic therapy following the paradigm of metronomic dosed chemotherapeutics combined with proapoptotic biomodulators had not been

considered previously in these patients. Therefore, in a pilot study, the efficacy of metronomically scheduled, low-dose trofosfamide in combination with the peroxisome proliferator-activated receptor gamma agonist, pioglitazone, and the selective cyclooxygenase-2 inhibitor, rofecoxib, was evaluated in patients with advanced vascular malignancies.

METHODS: Six patients with advanced and pretreated but progressive, malignant vascular tumors (5 angiosarcomas and 1 hemangioendothelioma) received a combination of pioglitazone (45 mg per day orally) plus rofecoxib (25 mg per day orally) and, after 14 days, trofosfamide (3 x 50 mg per day orally). The therapy was administered continuously until progression was observed. If necessary, doses were modified according to side effects.

RESULTS: Two patients responded with complete remission of disease, one patient responded with partial remission, and three patients achieved stabilization of disease (no change). The median progression-free survival was 7.7 months (range, 2-15 months). Side effects generally were mild (World Health Organization Grade 1-2). Hospitalization was not necessary.

CONCLUSIONS: This new triple combination of low-dose metronomic trofosfamide, pioglitazone, and rofecoxib may represent a feasible new alternative in the palliative treatment of patients with advanced malignant vascular tumors. Copyright 2003 American Cancer Society.

PMID: 14601096 [PubMed - indexed for MEDLINE]

7.2 Combinatie ifosfamide, vincristine, actinomycine D: zinvol?

Metastasized angiosarcoma of the spleen in a 2-year-old girl.

Pediatr Hematol Oncol. 2005 Jul-Aug;22(5):387-90

den Hoed ID, Granzen B, etal

Department of Paediatric Surgery, Paediatrics, and Pathology, University Hospital, Maastricht, The Netherlands.

Primary angiosarcoma of the spleen is rare and the prognosis is very poor. The authors present a 2-year-old girl with spontaneous rupture of splenic angiosarcoma. At diagnosis there were liver metastases. After splenectomy she received chemotherapy with ifosfamide, vincristine, and actinomycine D combined with a partial liver resection. She remained in complete remission over 2 years from diagnosis.

PMID: 16020128 [PubMed - indexed for MEDLINE]

7.3 Anthracycline en ifosfamide; weinig effectief

Metastatic angiosarcoma of the kidney: a case report with treatment approach and review of the literature.

J Chemother. 2006 Apr;18(2):221-4.

Berretta M, etal

Dipartimento di Oncologia Medica, Centro di Riferimento Oncologico, Aviano, Italy.

Angiosarcomas are rare soft tissue malignancies. Typically they originate from the skin of the scalp or face, whereas visceral sarcomas are very rare. We report the case of a 67-year-old man affected by a large angiosarcoma of the kidney. After surgical removal, a rapid peritoneal, visceral and cutaneous diffusion developed. Palliative chemotherapy, based on anthracycline and ifosfamide, which are normally used to treat all other high-grade spindle cell sarcomas, was totally inactive. On the basis of these results and of the biological characteristics of these rare neoplasms it is mandatory to develop other therapeutic approaches. Antiangiogenetic agents are of interest for this disease due to the peculiar origin of the cells of these sarcomas.

PMID: 16736893 [PubMed - in process]

7.4 Paclitaxel niet blijvend en Doxorubicine / ifosfamide weinig effectief

Primary temporal bone angiosarcoma: a case report.

J Neurooncol. 2005 Nov;75(2):121-5.

Scholsem M, Raket D, etal

Department of Neurosurgery, University Hospital of Liege, B-35, Sart-Tilman, 4000 Liege, Belgium. martin.scholsem@ulg.ac.be

We present a rare case of temporal bone angiosarcoma diagnosed in a 26-year-old female patient at 36 week of pregnancy. The patient was referred with a 2 months history of left otalgia and tinnitus with a tender swelling above the mastoid. Cranial imaging studies showed a 7 x 5 x 4 cm hypervascularized mass located in the left middle fossa with lysis of the temporal bone and extension to the subcutis.

After the baby was delivered by caesarean section, the patient entered the oncology protocol. Selective embolization of the feeding vessels was followed by gross total surgical resection using a combined supra- and infra-tentorial approach. Pathological findings were those of a poorly differentiated, highly malignant sarcoma with a large epitheloid component and immunohistochemical evidence of endothelial differentiation (CD31, Factor VIII related antigen, CD34), consistent with an angiosarcoma with epitheloid features. No extra-cranial tumor was found after extensive staging. The patient received adjuvant radiotherapy followed by a course of chemotherapy consisting of 6 cycles of paclitaxel. At 15 months follow-up, she developed multiple distant metastasis to a left postauricular lymph node and to the lungs and ribs. The patient was given a second line chemotherapy using doxorubicine and ifosfamide. Despite an initial good response, she died with metastatic disease 26 months after diagnosis. We present a rare case of primary temporal bone angiosarcoma and report our experience with a multimode therapeutic approach combining surgery, radiotherapy and chemotherapy.

PMID: 16132518 [PubMed - indexed for MEDLINE]

7.5 Metronomic trofosfamide; een case met goed resultaat

Complete remission of relapsing high-grade angiosarcoma with single-agent metronomic trofosfamide.

Anticancer Drugs. 2006 Sep;17(8):997-8.

Kopp HG, **Kanz L**, **Hartmann JT**.

Department of Medical Oncology, Medical Center II, South West German Cancer Center, Eberhard-Karls-University, Otfried-Mueller-Strasse 10, 72076 Tuebingen, Germany.

A limited repertoire of chemotherapeutics is available for the therapy of metastasizing angiosarcoma. Moreover, response rates are typically low and outcomes are unfavorable. Metronomically, dosed oral chemotherapy provides a convenient treatment option and surprisingly high response rates have been published for small patient groups. We report on a case from our clinic, in which a complete response with oral trofosfamide was achieved in a patient suffering from relapsed high-grade angiosarcoma metastasizing to the liver and lung. The patient experienced minimal side-effects from her trofosfamide treatment. Responses like this are encouraging and should make us rethink treatment approaches for metastasizing soft-tissue sarcoma. The mechanism of action of metronomic chemotherapy, although thought to be antiangiogenic in nature, is still unclear, as is the additive effect of angiogenic inhibitors like cyclooxygenase II inhibitors or peroxisome proliferator-activated receptor-gamma agonists. Prospective studies that include the examination of patient samples during treatment are ongoing in order to optimize further development of this novel therapeutic approach.

PMID: 16940811 [PubMed - indexed for MEDLINE]

7.6 Gebruik iridium(192) wire brachytherapy bij angiosarcoom in ooglid

Angiosarcoma of the eyelid and periorbital region. Experience in Leiden with iridium192 brachytherapy and low-dose doxorubicin chemotherapy.

Orbit. 2008 Mar;27(1):5-12

de Keizer RJ, **de Wolff-Rouendaal D**, **Nooy MA**.

Department of Opthalmology, Leiden University Medical Center, Leiden, The Netherlands.

AIM: To report on the use of iridium(192) brachytherapy and doxorubicin chemotherapy as adjuvant therapy in 6 patients with angiosarcoma of the eyelid and periorbital region.

MATERIAL AND METHODS: Tumor localization and diameter, signs of inflammation, histology and treatment are discussed in this retrospective study of 6 patients (age 46-87 yrs.) presenting with primary angiosarcoma in the eyelid.

RESULTS: Six patients (4 elderly) with angiosarcoma localized in one or more eyelids, the face or multilocular were seen between 1987 and 2000. In one patient, a small nodular tumor did not recur within 4 years after radical excision. In another patient, the tumor was treated with surgery and iridium(192) wire brachytherapy and did not recur in 17 years of follow-up. In four patients with large diffuse tumors that were treated with doxorubicin, partial regression was achieved. The follow-up was >3 years (median 5 years).

CONCLUSION: If radical surgery for angiosarcoma of the eyelid and periorbital region is not possible, adjuvant iridium(192) wire brachytherapy may prove beneficial. For widespread, diffusely growing tumors, and in elderly patients, low-dose (slowly, 20 mg i.v.) doxorubicin can be used weekly as adjuvant therapy, resulting in partial regression and longer survival rates than previously published by other authors.

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