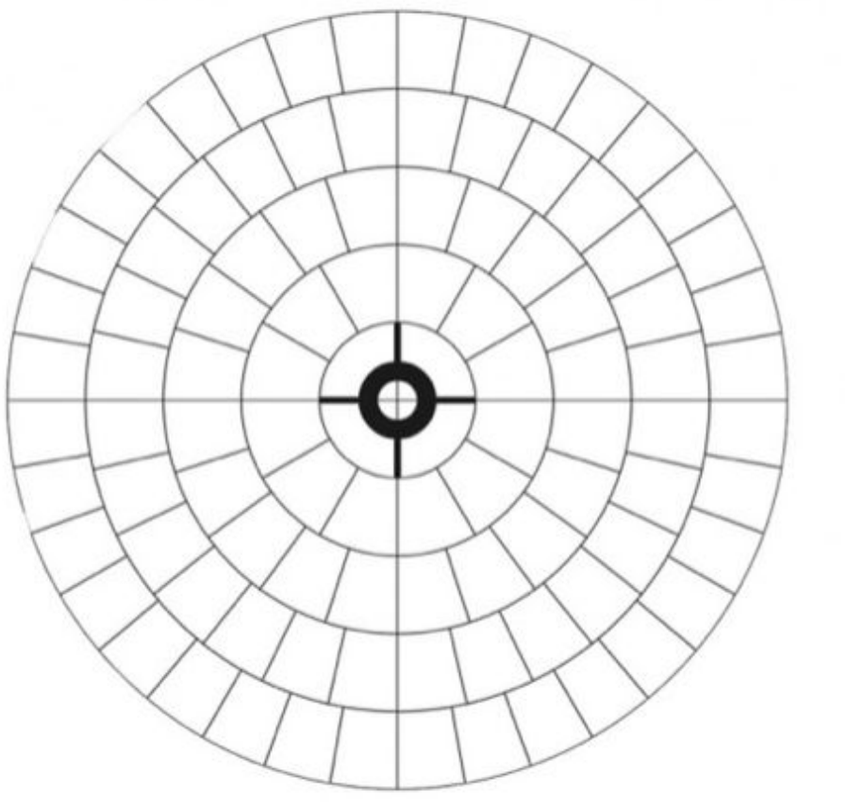
Таргетная противоопухолевая терапия

Разбор основных препаратов

Таргетная терапия

От английского target - цель, мишень. Относят к перспективным методам молекулярной медицины.
Таргетные лекарства очень специфичны и разрабатываются под конкретный мутировавший ген раковой клетки данного вида опухоли. Поэтому до таргетного лечения обязательно проводят генетическое исследование материала, взятого на биопсию.



Таргетная терапия

- Низкомолекулярные ингибиторы (Ингибиторы киназ)

- Моноклональные антитела

Мутация в гене C-Kit

- Когда мутирует ген, рецептор (белок) не нуждается в сигналах для размножения клетки, и клетки делятся бесконтрольно сами по себе.

- Прогностический фактор паттерн локализация трансмембрального белка KIT

- Гистологическая организация. Митотический индекс. (играет не меньшую роль в построении прогнозов)

Prognostic and predictive significance of KIT protein expression and *c-kit* gene mutation in canine cutaneous mast cell tumours: A consensus of the Oncology-Pathology Working Group

Douglas H. Thamm[1] | Anne C. Avery[1] | Davide Berlato[2] | Julie Bulman-Fleming[3] | Craig A. Clifford[4] | A. Elizabeth Hershey[5] | Joanne L. Intile[6] | Pamela D. Jones[7] | Debra A. Kamstock[8] | Julius M. Liptak[9] | Alana Pavuk[10] | John Peauroi[11] | Roger Powell[12] | Kerry Rissetto[13] | Victor E. O. Valli[11] | Joshua D. Webster[14]

Малые молекулы у собак

- Тоцераниба фосфат
- Маситиниб мезилаб
- Иматиниб мезилаб

низкомолекулярный ингибитор, блокирующий сигналы рецепторных тирозинкиназ VEGFR2, PDGFRα/β, Kit и CSF1R. Благодаря своей способности блокировать сигналы KIT, препарат обладает достоверной активностью против мастоцитом с активирующими мутациями KIT. Однако изначально он разрабатывался в качестве антиангиогенного препарата, так как обладает способностью подавлять VEGFR (рецептор фактора роста эндотелия сосудов) и PDGFR (рецептор тромбоцитарного фактора роста) и, следовательно, более широким спектром активности в отношении ряда солидных опухолей, таких как карцинома щитовидной железы и аденокарцинома апокринных желез анальных пазух.

Phase I Dose-Escalating Study of SU11654, a Small Molecule Receptor Tyrosine Kinase Inhibitor, in Dogs with Spontaneous Malignancies[1,2]

Cheryl A. London,[3] Alison L. Hannah, Regina Zadovoskaya, May B. Chien, Cynthia Kollias-Baker, Mona Rosenberg, Sue Downing, Gerald Post, Joseph Boucher, Narmada Shenoy, Dirk B. Mendel, Gerald McMahon, and Julie M. Cherrington

School of Veterinary Medicine, University of California, Davis, Davis, California 95616 [C. A. L., R. Z., M. B. C., C. K-B.]; Veterinary Cancer Referral Group, Los Angeles, California [M. R., S. D.]; Veterinary Cancer Referral Group, New York, New York [G. P.]; SUGEN, Inc., South San Francisco, California [A. L. H., N. S., D. B. M., G. M., J. M. C.]; and Pharmacia Animal Health, Kalamazoo, Michigan [J. B.]

mas (n = 2), soft tissue sarcomas (n = 2), and multiple myeloma (n = 1), for an overall response rate of 28% (16 of 57). Stable disease of sufficient duration to be considered clinically meaningful (>10 weeks) was seen in an additional 15 dogs, for a resultant overall biological activity of 54% (31 of 57).

***Conclusions*: This study provides the first evidence that p.o. administered kinase inhibitors can exhibit activity against a variety of spontaneous malignancies. Given the similarities of canine and human cancers with regard to tumor biology and the presence of analogous RTK dysregulation, it is likely that such agents will demonstrate comparable antineoplastic activity in people.**

Выводы

- Биологическая активность 56%
- Полный ответ 6 случаев
- Частичный ответ 10 случаев
- Стабилизация заболевания 15 случаев

Применимость

Cancer Therapy: Clinical

Multi-center, Placebo-controlled, Double-blind, Randomized Study of Oral Toceranib Phosphate (SU11654), a Receptor Tyrosine Kinase Inhibitor, for the Treatment of Dogs with Recurrent (Either Local or Distant) Mast Cell Tumor Following Surgical Excision

Cheryl A. London,[1] Phyllis B. Malpas,[2] Stacey L. Wood-Follis,[2] Joseph F. Boucher,[2] Anthony W. Rusk,[3] Mona P. Rosenberg,[4] Carolyn J. Henry,[5] Kathy L. Mitchener,[6] Mary K. Klein,[7] John G. Hintermeister,[8] Philip J. Bergman,[9] Guillermo C. Couto,[10] Guy N. Mauldin,[11] and Gina M. Michels[2]

- Аденокарцинома апокри[illegible]

- Метастатическая остеосаркома

- Карцинома щитовидной железы

Original Article

jfms Journal of Feline Medicine and Surgery

Retrospective evaluation of toceranib phosphate (Palladia) in cats with oral squamous cell carcinoma

Journal of Feline Medicine and Surgery
1–9

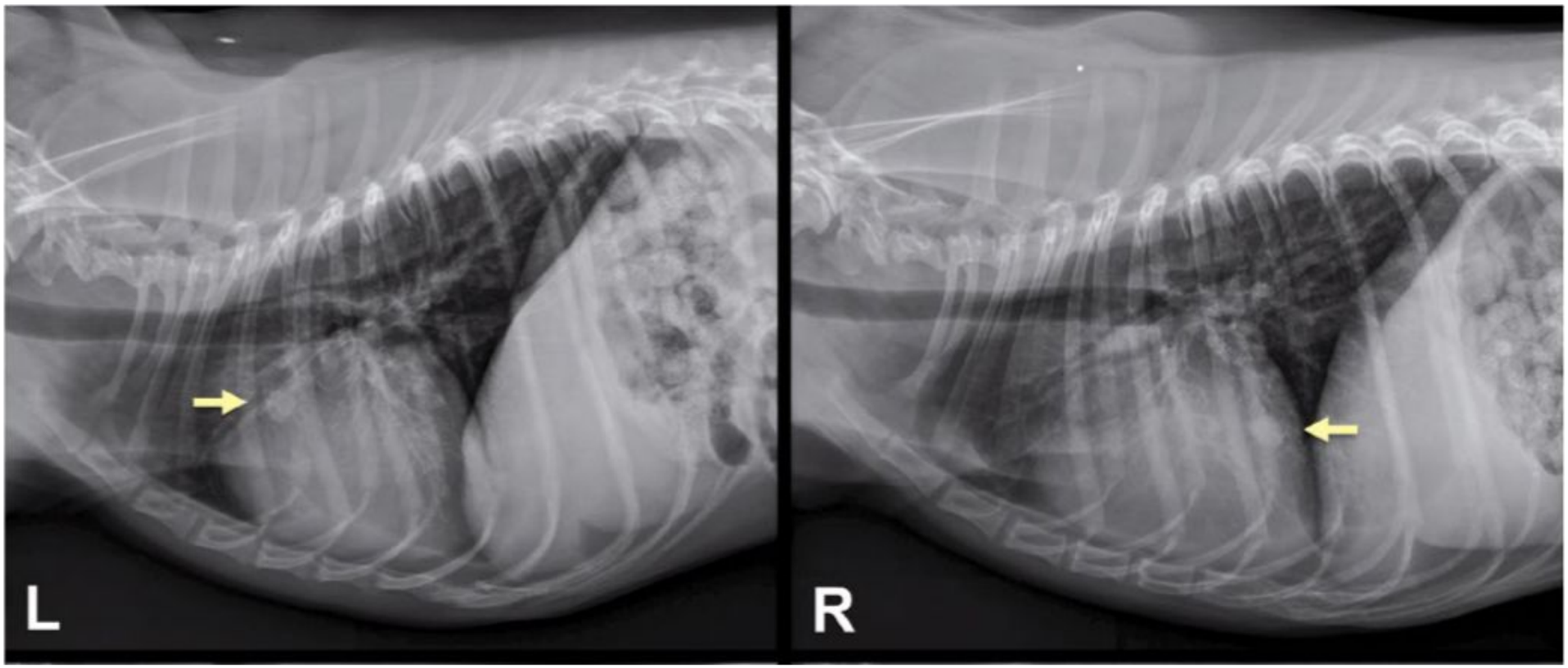
DOI: 10.1177/1098612X15622237
jfms.com
SAGE

Valerie Wiles[1,2], Ann Hohenhaus[1], Kenneth Lamb[3], Bushra Zaidi[1], Maria Camps-Palau[1] and Nicole Leibman[1]

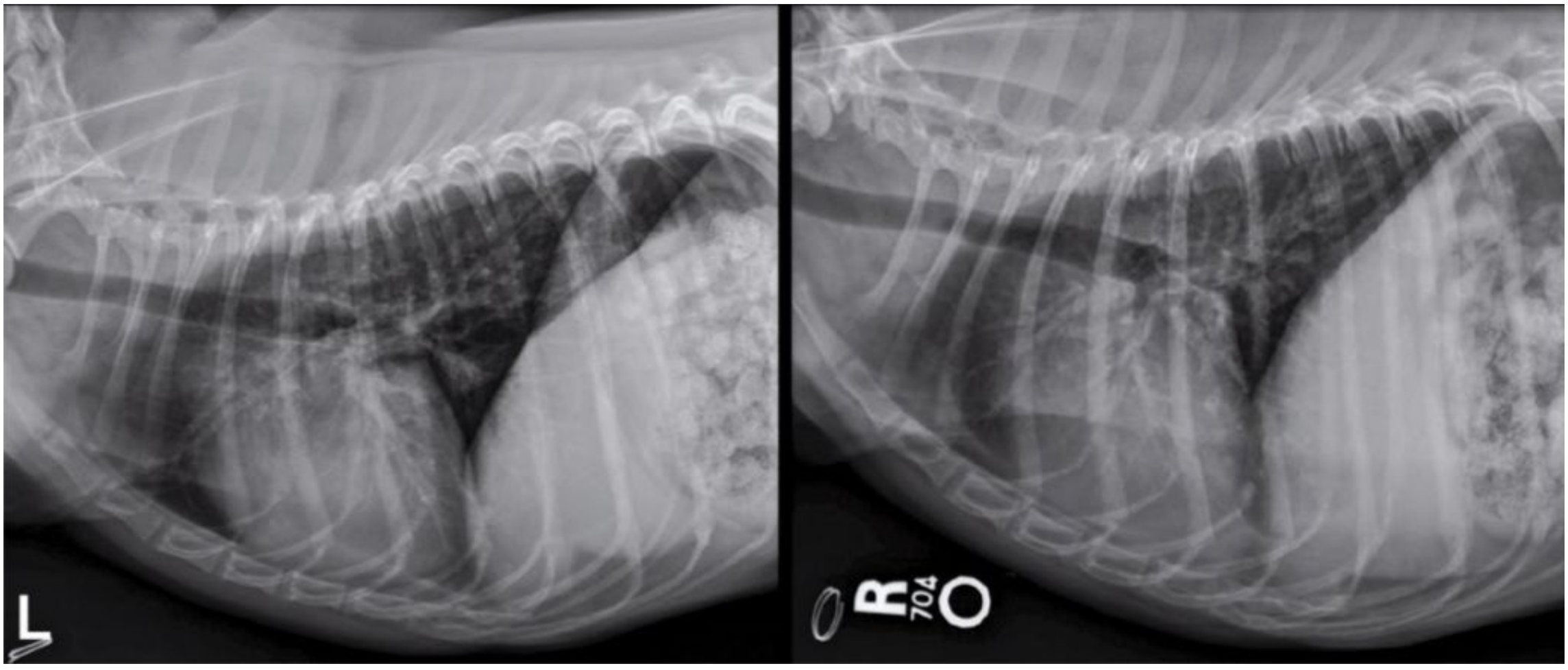
Ответ на терапию тоцеранибом у собаки с метастатической карциномой щитовидной железы.

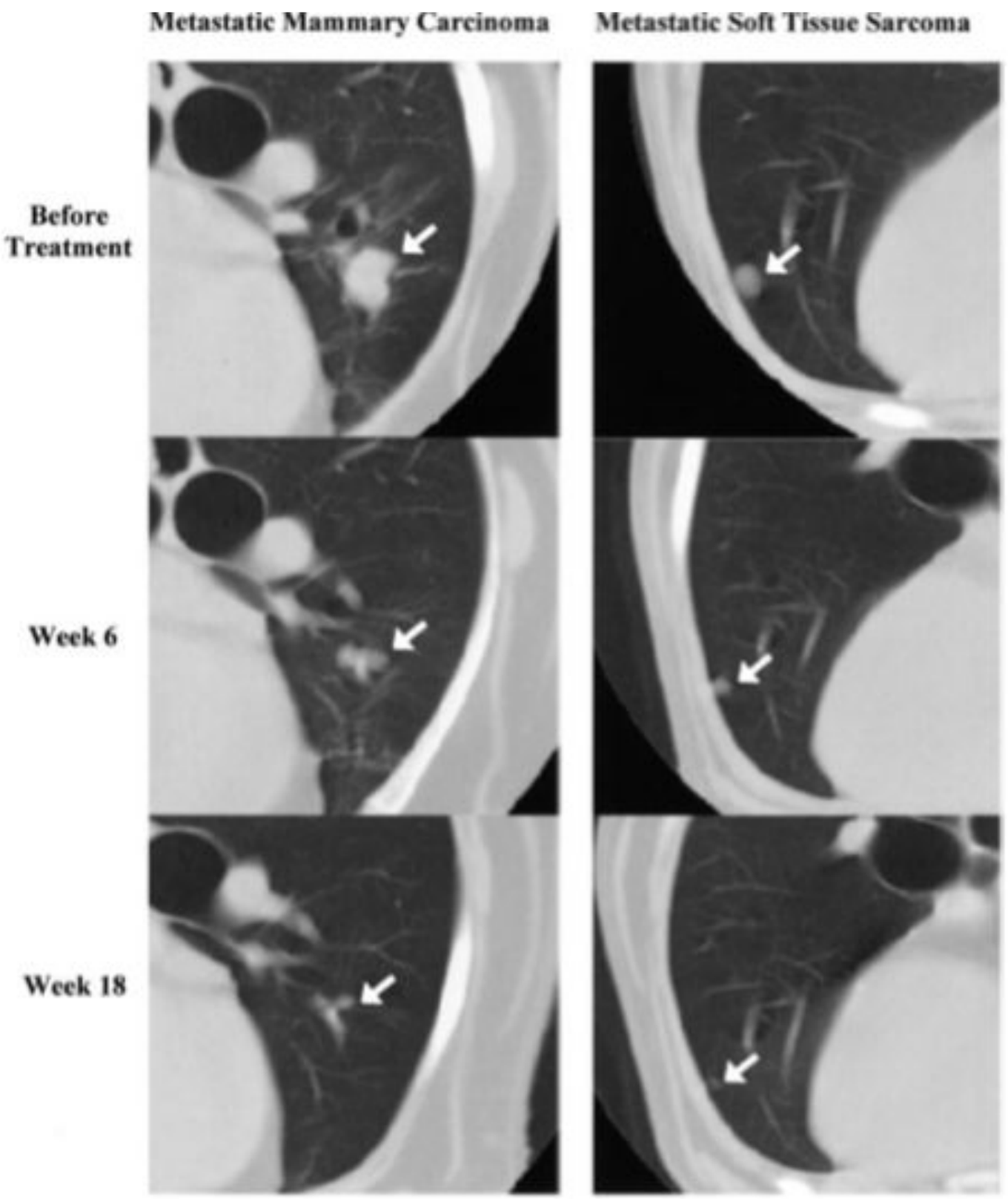
Рентгенограммы грудной клетки в боковой проекции демонстрируют метастатические узлы в легких (стрелки) до начала лечения и через 3 месяца после начала терапии тоцеранибом

До лечения



После лечения




Metastatic Mammary Carcinoma
Metastatic Soft Tissue Sarcoma
Before Treatment
Week 6
Week 18

Применимость тоцераниба при МСТ в комплексе с другими противоопухолевыми агентами

Комплексное применение винбластина и тоцераниба при МСТ

МПД Винбластин - 1,6 мг/м^2

МПД Тоцераниб - 3,25 мг/кг при введении каждые 48 ч.

ДЛТ - нейтропения

ЧОО - 71%

МТД ломустина 50 мг/м каждые 3 недели при сочетанном введении с

Тоцераниб 2.75 мг/кг ЧОО (38,4 %)

Ломустин и тоцераниб (в дни 1, 3 и 5 21-дневного цикла)

МПД CCNU - 50 мг/м^2, вводившимся на 3-й день каждого цикла, привело к ЧОО 46 % при терапии неоперабельной

МСТ

ДЛТ - нейтропения.

Тоцераниб в сочетании с лучевой терапией

МПД Тоцераниб 2,75 мг/кг в понедельник, среду и пятницу в сочетании с омепразолом, дифенгидрамином и преднизоном (1 мг/кг один раз в сутки) в течение 1 недели

РТ - крупнофракционная лучевая терапия (4 фракции по 6 Гр один раз в неделю).

ЧОО составила 76,4 %

Применимость тоцераниба в комбинации с РТ при SCC носа

В этом исследовании у собак, получавших только курс лучевой терапии, среднее время выживания составило 371 день, в сравнении с 615 днями у животных, получавших также и тоцераниб, что подтверждает преимущества комбинированной терапии для собак с этим типом опухолей.

(Ehling T, Klein M, Smith L, A multi-center VRTOG stu b phospha as a primary and/or adjuvant agent in the treatment o

Маситиниб мезилат

Маситиниб представляет собой низкомолекулярный ингибитор, блокирующий Kit, PDGFR

Биологическая активность маситиниба была продемонстрирована в рандомизированном двойном слепом плацебо-контролируемом клиническом исследовании фазы 3 на 202 собаках с неоперабельной МСТ 2-й и 3-й стадий

Masitinib is Safe and Effective for the Treatment of Canine Mast Cell Tumors

K.A. Hahn, G. Oglivie, T. Rusk, P. Devauchelle, A. Leblanc, A. Legendre, B. Powers, P.S. Leventhal, J.-P. Kinet, F. Palmerini, P. Dubreuil, A. Moussy, and O. Hermine

Background: Activation of the KIT receptor tyrosine kinase is associated with the development of canine mast cell tumors (MCT).

Hypothesis/Objective: To evaluate the efficacy of masitinib, a potent and selective inhibitor of KIT, in the treatment of canine MCT.

Animals: Two hundred and two client-owned dogs with nonmetastatic recurrent or nonresectable grade II or III MCT.

Methods: Double-blind, randomized, placebo-controlled phase III clinical trial. Dogs were administered masitinib (12.5 mg/kg/d PO) or a placebo. Time-to-tumor progression (TTP), overall survival, objective response at 6 months, and toxicity were assessed.

Resulsts: Masitinib increased overall TTP compared with placebo from 75 to 118 days ($P = .038$). This effect was more pronounced when masitinib was used as first-line therapy, with an increase in the median TTP from 75 to 253 days ($P = .001$) and regardless of whether the tumors expressed mutant (83 versus not reached [$P = .009$]) or wild-type KIT (66 versus 253 [$P = .008$]). Masitinib was generally well tolerated, with mild (grade I) or moderate (grade II) diarrhea or vomiting as the most common adverse events.

Conclusions and Clinical Importance: Masitinib is safe and effective at delaying tumor progression in dogs presenting with recurrent or nonresectable grade II or III nonmetastatic MCT.

Key words: Dog; KIT; Mast cell tumor.

Хотя достоверного повышения частоты ответов на введение маситиниба у собак с мутациями гена Kit и без таковых относительно плацебо не наблюдалось, время до прогрессирования заболевания (ВПЗ) было достоверно выше у собак, получавших маситиниб (118 дней против 75 дней).

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Evaluation of 12- and 24-month survival rates after treatment with masitinib in dogs with nonresectable mast cell tumors

Kevin A. Hahn, DVM, PhD; Alfred M. Legendre, DVM, MS; Neil G. Shaw, DVM; Brenda Phillips, DVM; Gregory K. Ogilvie, DVM; Deborah M. Prescott, DVM, PhD; Stephen W. Atwater, DVM, MS; Janet K. Carreras, DVM; Susan E. Lana, DVM, MS; Tracy Ladue, DVM, MS; Anthony Rusk, DVM; Jean Pierre Kinet, MD; Patrice Dubreuil, PhD; Alain Moussy, MBA; Olivier Hermine, MD, PhD

В последующем исследовании на 139 собаках с неоперабельной МСТ 2-й и 3-й степени было продемонстрировано, что у собак, получавших маситиниб, долгосрочный контроль заболевания достоверно улучшался: через 2 года 36 % проходивших лечение животных были живы, в сравнении с 15 % среди собак, не получавших маситиниб.

P.S. Также отмечалась активность препарата в отношении Т-клеточной лимфомы собак, хотя формальных клинических исследований по этому заболеванию не проводилось.

Journal of Veterinary Internal Medicine
Open Access

J Vet Intern Med 2015;29:1098–1104

Pulse-Administered Toceranib Phosphate Plus Lomustine for Treatment of Unresectable Mast Cell Tumors in Dogs

J.H. Burton, R.O. Venable, D.M. Vail, L.E. Williams, C.A. Clifford, S.M. Axiak-Bechtel, A.C. Avery, and D.H. Thamm

Background: Nonresectable mast cell tumors (MCT) in dogs remain a therapeutic challenge, and investigation of novel combination therapies is warranted. Intermittent administration of tyrosine kinase inhibitors (TKI) combined with cytotoxic chemotherapy may effectively chemosensitize canine MCT while decreasing cost and adverse effects associated with either agent administered as monotherapy.

Hypothesis/Objectives: The primary study objectives were to (1) identify the maximally tolerated dose (MTD), (2) determine the objective response rate (ORR) and (3) describe the adverse event profile of pulse-administered toceranib phosphate (TOC) combined with lomustine.

Animals: Forty-seven client-owned dogs with measurable MCT.

Methods: Toceranib phosphate was given PO on days 1, 3 and 5 of a 21-day cycle at a target dosage of 2.75 mg/kg. Lomustine was given PO on day 3 of each cycle at a starting dosage of 50 mg/m^2. All dogs were concurrently treated with diphenhydramine, omeprazole, and prednisone.

Results: The MTD of lomustine was established at 50 mg/m^2 when combined with pulse-administered TOC; the dose-limiting toxicity was neutropenia. Forty-one dogs treated at the MTD were evaluable for outcome assessment. The ORR was 46% (4 complete response, 15 partial response) and the overall median progression-free survival (PFS) was 53 days (1 to >752 days). On multivariate analysis, variables significantly associated with improved PFS included response to treatment, absence of metastasis, and no previous chemotherapy.

Conclusions and clinical importance: Combined treatment with pulse-administered TOC and lomustine generally is well tolerated and may be a reasonable treatment option for dogs with unresectable or metastatic MCT.

Key words: Cancer; Chemotherapy; Dog; Tyrosine kinase inhibitor.

Однако в исследовании только у одного из пяти пациентов с мутациями c-kit был рецидив заболевания и летальный исход, связанный с МСТ.

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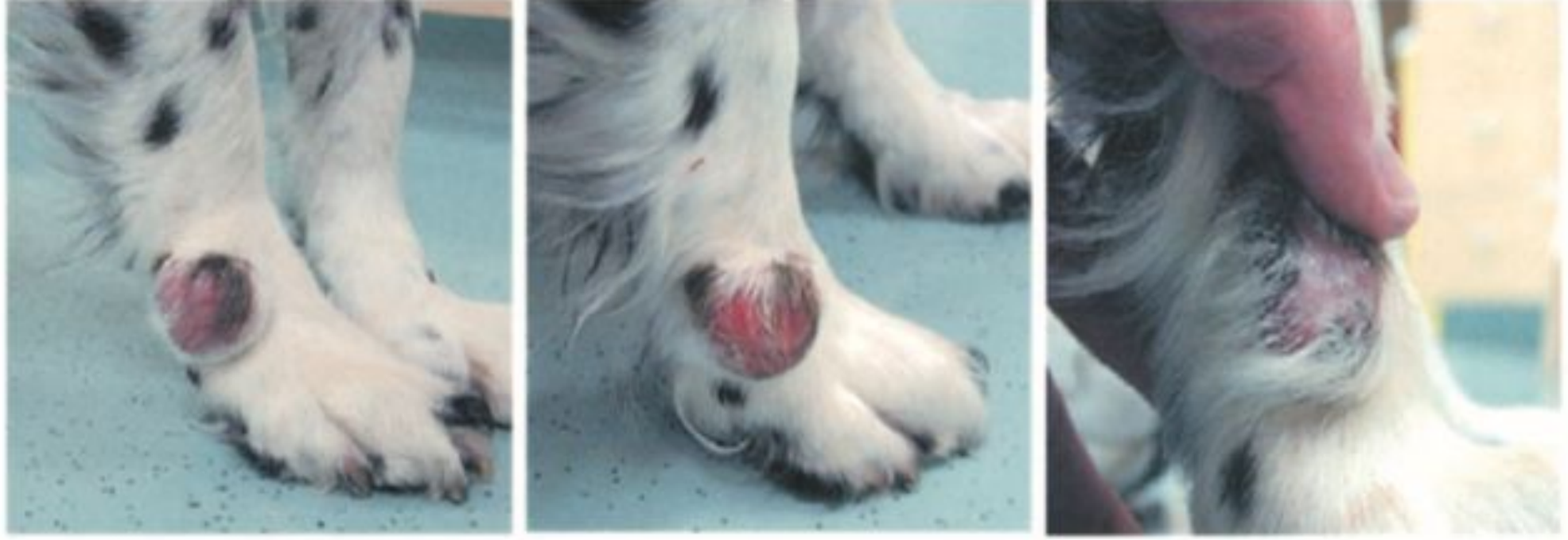
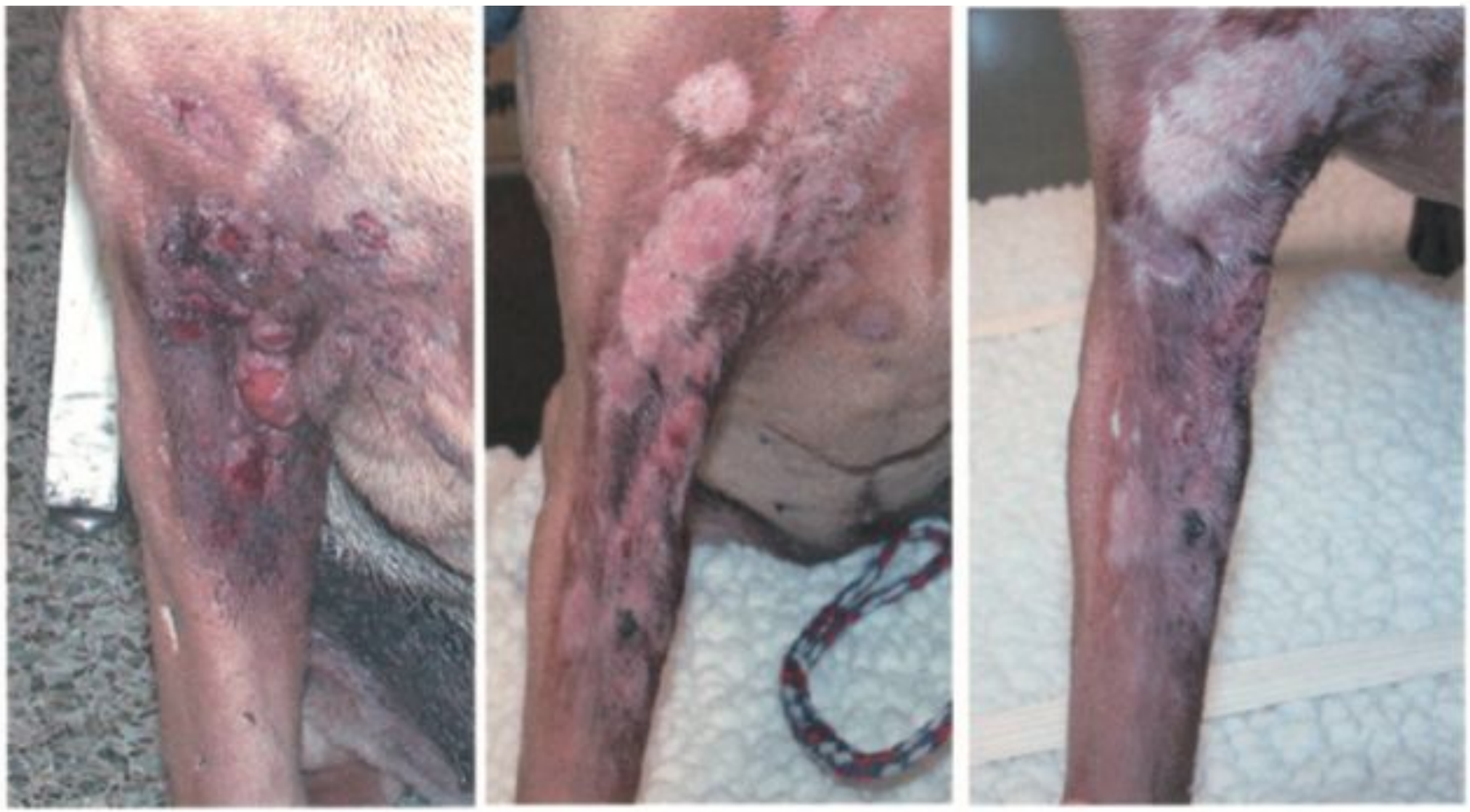
Conclusions and Clinical Importance: Masitinib is safe and effective at delaying tumor progression in dogs presenting with recurrent or nonresectable grade II or III nonmetastatic MCT.

Key words: Dog; KIT; Mast cell tumor.

Снижение эффективности Маситиниба при назначении после предшествующих противоопухолевой терапии или лучевой терапии





Evaluation of 12- and 24-month survival rates after treatment with masitinib in dogs with nonresectable mast cell tumors

Kevin A. Hahn, DVM, PhD; Alfred M. Legendre, DVM, MS; Neil G. Shaw, DVM; Brenda Phillips, DVM; Gregory K. Ogilvie, DVM; Deborah M. Prescott, DVM, PhD; Stephen W. Atwater, DVM, MS; Janet K. Carreras, DVM; Susan E. Lana, DVM, MS; Tracy Ladue, DVM, MS; Anthony Rusk, DVM; Jean Pierre Kinet, MD; Patrice Dubreuil, PhD; Alain Moussy, MBA; Olivier Hermine, MD, PhD

Objective—To evaluate the effectiveness of masitinib for the treatment of nonresectable mast cell tumors (MCTs) in dogs at 12 and 24 months after onset of treatment.

Animals—132 dogs with nonresectable grade 2 or 3 MCTs.

Procedures—Dogs received masitinib (12.5 mg/kg/d, PO; n = 106) or a placebo (26). After 6 months, treatment was extended with tumor assessments at 3-month intervals until detection of disease progression. Endpoints were tumor response and overall survival rate and time.

Results—In dogs with nonresectable MCTs, masitinib significantly improved survival rate, compared with results for the placebo, with 59 of 95 (62.1%) and 9 of 25 (36.0%) dogs alive at 12 months and 33 of 83 (39.8%) and 3 of 20 (15.0%) dogs alive at 24 months, respectively. Median overall survival time was 617 and 322 days, respectively. Tumor control at 6 months had a high predictive value for 24-month survival, with high specificity (88%) and sensitivity (76%), whereas short-term tumor response (within 6 weeks) had a poor predictive value. Complete responses at 24 months were observed in 6 of 67 (9.0%) dogs with nonresectable MCTs treated with masitinib.

Conclusions and Clinical Relevance—Masitinib significantly increased survival rates at 12 and 24 months in dogs with nonresectable MCTs. Control of disease at 6 months, but not best response at 6 weeks, was predictive of long-term survival in dogs treated with masitinib, which suggested that short-term response may be irrelevant for assessing clinical efficacy of tyrosine kinase inhibitors for treatment of MCTs. (*Am J Vet Res* 2010;71:1354–1361)

- Отсутсвие мутации в гене C-Kit

- 200 случаев показали, что частота этого типа мутации KIT составляет приблизительно 5% среди GIST

CHIC2 deletion, a surrogate for FIP1L1-PDGFRA fusion, occurs in systemic mastocytosis associated with eosinophilia and predicts response to imatinib mesylate therapy.

Pardanani A[1], Ketterling RP, Brockman SR, Flynn HC, Paternoster SF, Shearer BM, Reeder TL, Li CY, Cross NC, Cools J, Gilliland DG, Dewald GW, Tefferi A.

⊕ **Author information**

Abstract

Imatinib mesylate is effective in the treatment of hematologic malignancies that are characterized by either abl- or PDGFR beta-activating mutations. The drug is also active in a subset of patients with eosinophilic disorders and systemic mast cell disease (SMCD). Recently, a novel tyrosine kinase that is generated from fusion of the Fip1-like 1 (FIP1L1) and PDGFR alpha (PDGFRA) genes has been identified as a therapeutic target for imatinib mesylate in hypereosinophilic syndrome (HES). We used fluorescence in situ hybridization (FISH) to detect deletion of the CHIC2 locus at 4q12 as a surrogate for the FIP1L1-PDGFRA fusion. CHIC2 deletion was observed in bone marrow cells for 3 of 5 patients with SMCD associated with eosinophilia. Deletion of this locus and expression of the FIP1L1-platelet-derived growth factor receptor alpha (PDGFRA) fusion was also documented in enriched eosinophils, neutrophils, or mononuclear cells by both FISH and reverse transcriptase-polymerase chain reaction (RT-PCR) for one patient. While all 3 patients with the FIP1L1-PDGFRA rearrangement achieved a sustained complete response with imatinib mesylate therapy, the other two, both carrying the c-kit Asp816 to Val (Asp816Val) mutation, did not. These observations suggest that the FIP1L1-PDGFRA rearrangement occurs in an early hematopoietic progenitor and suggests that the molecular pathogenesis for a subset of SMCD patients is similar to that of HES. Screening for the FIP1L1-PDGFRA rearrangement and Asp816Val mutation will advance rational therapy decisions in SMCD.

Seminars in Diagnostic Pathology (2006) 23, 91-102

ELSEVIER

Seminars in Diagnostic Pathology

KIT and PDGFRA mutations in gastrointestinal stromal tumors (GISTs)

Jerzy Lasota, MD, Markku Miettinen, MD

Применимость при других опухолевых поражениях

- Меланомы (беспигментные)
- GIST
- Фибросаркомы ротовой полости у собак
- ТСС мочевого пузыря у собак (в комбинации с ингибиторами COX)
- Эпителиотропная лимфома собак
- Крупноклеточная лимфома кошек

Seminars in Diagnostic Pathology (2006) 23, 91-102

Seminars in Diagnostic Pathology

ELSEVIER

KIT and PDGFRA mutations in gastrointestinal stromal tumors (GISTs)

Jerzy Lasota, MD, Markku Miettinen, MD

From the Department of Soft Tissue Pathology, Armed Forces Institute of Pathology, Washington, DC.

Drug Design, Development and Therapy

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ORIGINAL RESEARCH

Cyclooxygenase inhibitors potentiate receptor tyrosine kinase therapies in bladder cancer cells in vitro

Masitinib monotherapy in canine epitheliotropic lymphoma.

Holtermann N[1], Kiupel M[2], Kessler M[3], Teske E[4], Betz D[5], Hirschberger J[1].

Author information

Abstract

This study evaluated efficacy and side effects of masitinib in canine epitheliotropic lymphoma. Complete remission occurred in 2 of 10 dogs and lasted for median 85 days. Five dogs went into partial remission for median 60.5 days. Three pretreated dogs did not respond to therapy. Side effects occurred in six dogs and were mostly mild to moderate. Immunohistochemistry was available for eight dogs. KIT receptor was negative in all of them, six of eight lymphomas stained strongly positive for stem cell factor (SCF). platelet-derived growth factor (PDGF)-AA was weakly positive in two and negative in six. PDGF-BB was negative in four tumours, weakly positive in one and strongly positive in three. One was strongly positive for PDGF receptor (PDGFR)-β, seven were negative for that receptor. Five showed strong expression of PDGFR-α, two showed weak expression, one was negative. In conclusion, masitinib is effective in treating canine epitheliotropic lymphoma. But its effects are most likely not generated through the KIT receptor.

Large granular lymphoma in six cats.

Sapierzyński R, Jankowska U, Jagielski D, Kliczkowska-Klarowicz K.

Abstract

Large granular lymphomas (LGLs) comprise a specific group of lymphomas regardless of classifi- cation scheme. An LGL consists of cells that show less or more mature morphology, but typically neoplastic cells possess cytoplasmic azurophilic granules clearly visible during cytological examin- ation. The aim of the present study was to present clinical and cytological data on large granular lymphomas in cats and to analyses the therapeutic responses in treated cases. During the period from 2012 to 2014 six cats were as having large granular lymphoma. In one cat a nasal form of LGL was recognized, a systemic form was recognized in another cat, and in four cases an alimentary form was recognized. Cellular samples for cytopathology were collected from the cat with nasal cavity mass, from the enlarged mandibular lymph node and thoracic cavity from second cat, and in four cats from the abdominal mass during ultrasound-assisted fine-needle biopsy. Therapy was introduced in 5 of the 6 cats. In two cases palliative therapy with glucocorticoids was conducted, in two cases chemotherapy with COP protocol, and therapy with masitinib in one case. The median of survival time for cats treated with anticancer therapy was 9 months, the median of survival time for cats treated with glucocorticoids was 1.5 months. In conclusion, large granular lymphomas, especially the alimentary form, are a relatively common type of lymphoma in cats. Simple diagnostic methods such as clinical examination, imaging techniques and routine cytology are sufficient in majority of cases. Despite aggressive behavior and poor general prognosis, conventional chemotherapy lead to a good response in some treated cats regardless of anatomic form and histologic grade of malignancy.

Иматиниб мезилат

Иматиниб является низкомолекулярным ингибитором и обладает активностью в отношении Bcr-Abl, Kit и PDGFR. Иматиниб разработан для лечения хронического миелолейкоза (ХМЛ) у человека, с отмечавшейся частотой ответа до 90 %, а в ветеринарной медицине применяется вне зарегистрированных показаний.

Десять из 21 собаки (48%) имели положительный ответ на лечение мезилатом иматиниба в течение 14 дней после начала лечения. Все 5 собак с явной мутацией c-kit ответили на препарат (1 полная ремиссия, 4 частичная ремиссия).

Effect of tyrosine kinase inhibition by imatinib mesylate on mast cell tumors in dogs.

Isotani M[1], Ishida N, Tominaga M, Tamura K, Yagihara H, Ochi S, Kato R, Kobayashi T, Fujita M, Fujino Y, Setoguchi A, Ono K, Washizu T, Bonkobara M.

⊕ Author information

Abstract

BACKGROUND: Imatinib mesylate is a small molecule targeted at dysregulated protein-tyrosine kinase. Mutation of c-kit exon 11, which induces constitutive phosphorylation of KIT, is one of the mechanisms for the development or progression of mast cell tumor (MCT) in dogs. The purpose of this study was to examine the therapeutic potential of imatinib mesylate in canine MCT.

HYPOTHESIS: Imatinib mesylate has activity against MCT in dogs, and response to treatment can be correlated to presence of mutation within exon 11 of c-kit.

ANIMALS: Twenty-one dogs with MCT with gross tumor burden and median tumor size of 7.2 cm (range, 1.0-25.3 cm) before treatment.

METHODS: Tumors were analyzed for mutation of c-kit exon 11. Imatinib mesylate was administered PO to the dogs at a dose of 10 mg/kg daily for 1-9 weeks.

RESULTS: Ten of 21 dogs (48%) had some beneficial response to imatinib mesylate treatment within 14 days of treatment initiation. All 5 dogs with a demonstrable c-kit mutation in exon 11 responded to the drug (1 complete remission, 4 partial remission).

CONCLUSIONS AND CLINICAL IMPORTANCE: Imatinib mesylate has clinical activity against MCT in dogs. Response could not be predicted based on presence of absence of a mutation in exon 11 of c-kit.

Хотя препарат не проходил оценку в проспективных клинических исследованиях, его противоопухолевая активность была продемонстрирована и на кошках, и на собаках. Объективные ответы наблюдались после терапии иматинибом собак с МСТ (как с мутациями KIT, так и без таковых); в одном исследовании у 10 из 21 собаки с МСТ, получавших иматиниб, опухоли сокращались, при этом ответ наблюдался у всех собак с внутренними тандемными дупликациями KIT (4 ПО, 1 ЧО)

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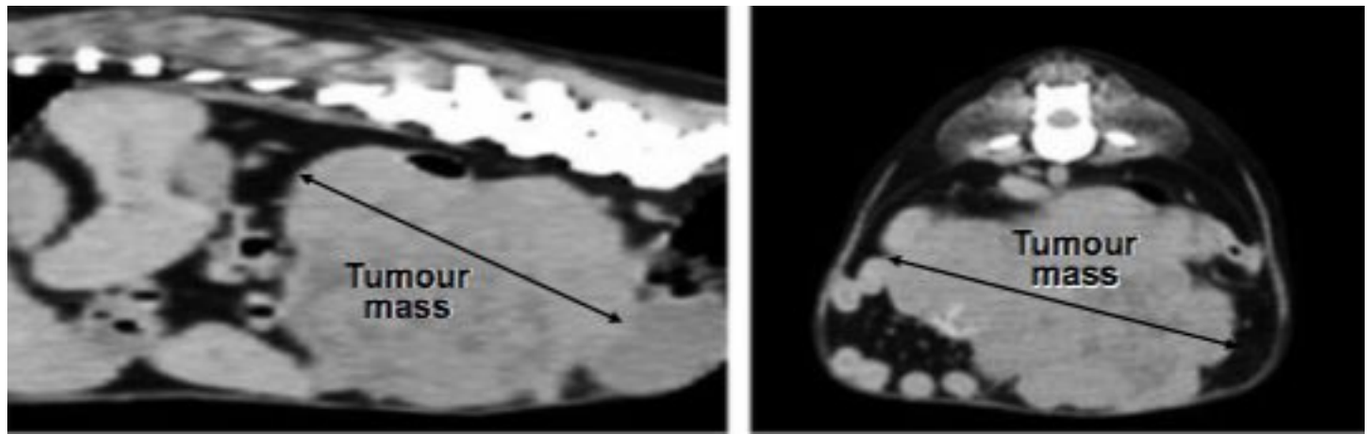
Short Communication

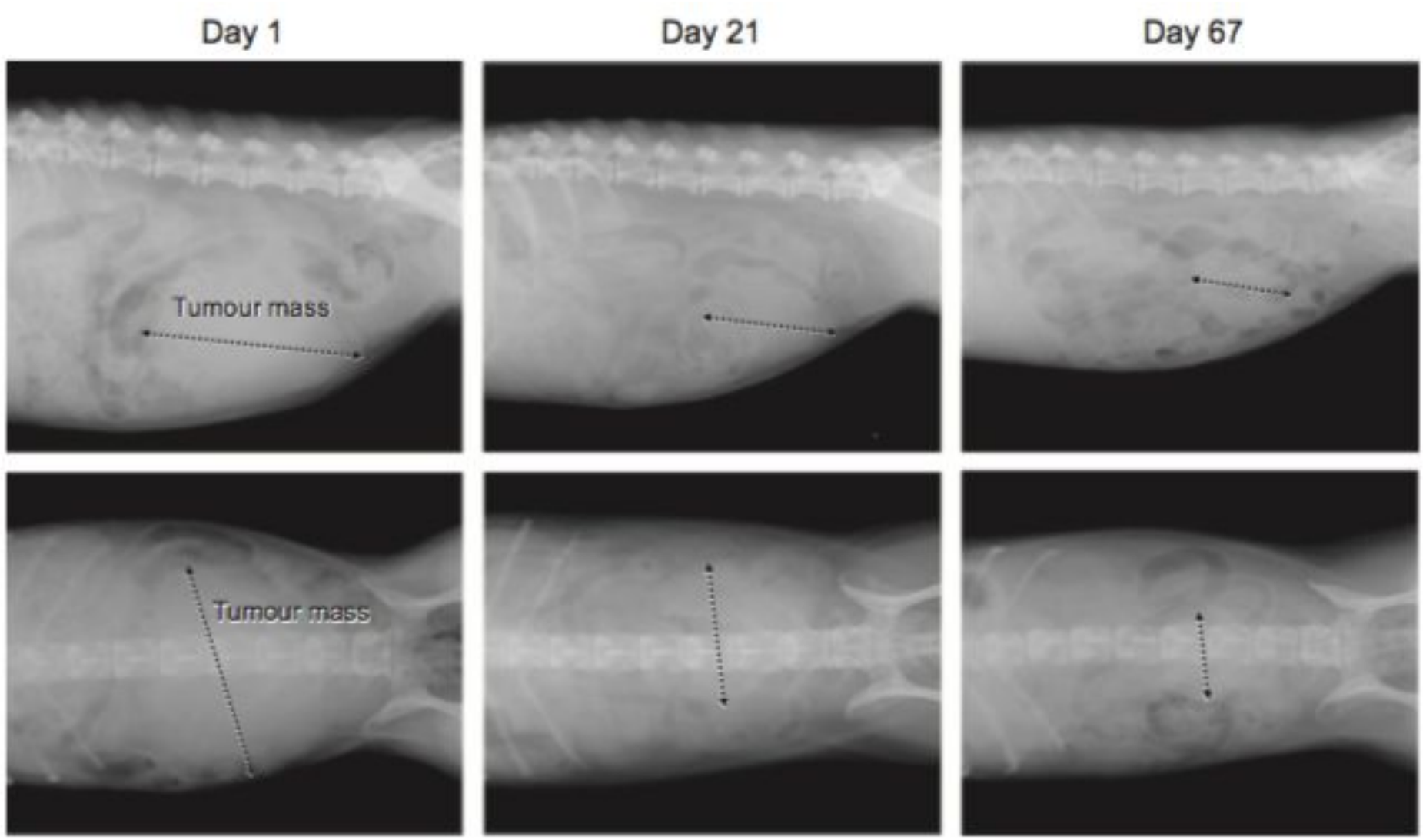
Imatinib-associated tumour response in a dog with a non-resectable gastrointestinal stromal tumour harbouring a *c-kit* exon 11 deletion mutation

Masato Kobayashi [a], Shiori Kuroki [a], Keita Ito [a], Akiko Yasuda [b], Harumi Sawada [b], Kenichiro Ono [a,c], Tsukimi Washizu [a], Makoto Bonkobara [a,*]

Кроме того, ответ на терапию иматинибом показала одна собака с неоперабельной гастроинтестинальной стромальной опухолью с мутацией KIT. Исходя из описанных случаев применения иматиниба для кошек и собак, вполне вероятно, что клинические ответы тесно связаны со статусом мутации гена Kit.

Иматиниб и GIST





Однако отмечались и случаи ответов на терапию при отсутствии этой мутации, что подразумевает другие механизмы дисрегуляции киназы. К примеру, мутации PDGFRα/β регистрировались в случаях реагирующего на иматиниб системного мастоцитоза и гастроинтестинальных стромальных опухолей в отсутствие сопутствующих мутаций гена Kit

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KIT and PDGFRA mutations in gastrointestinal stromal tumors (GISTs)

Jerzy Lasota, MD, Markku Miettinen, MD

From the Department of Soft Tissue Pathology, Armed Forces Institute of Pathology, Washington, DC.

Моноклональные антитела

- Ритуксимаб (используется в гуманной медицине в сочетании с химиопрепаратами при В-клеточной неходжкинской лимфоме человека, ассоциированной с трансмембранным антигеном CD20, что дополнительно провоцирует лизис опухолевых клеток.) При исследовании IN VITRO не показал своей эффективности

- Tanovea (не доступен в РФ)

Phase I Dose-Escalating Study of SU11654, a Small Molecule Receptor Tyrosine Kinase Inhibitor, in Dogs with Spontaneous Malignancies[1,2]

Cheryl A. London,[3] Alison L. Hannah, Regina Zadovoskaya, May B. Chien, Cynthia Kollias-Baker, Mona Rosenberg, Sue Downing, Gerald Post, Joseph Boucher, Narmada Shenoy, Dirk B. Mendel, Gerald McMahon, and Julie M. Cherrington

School of Veterinary Medicine, University of California, Davis, Davis, California 95616 [C. A. L., R. Z., M. B. C., C. K-B.]; Veterinary Cancer Referral Group, Los Angeles, California [M. R., S. D.]; Veterinary Cancer Referral Group, New York, New York [G. P.]; SUGEN, Inc., South San Francisco, California [A. L. H., N. S., D. B. M., G. M., J. M. C.]; and Pharmacia Animal Health, Kalamazoo, Michigan [J. B.]

mas ($n = 2$), soft tissue sarcomas ($n = 2$), and multiple myeloma ($n = 1$), for an overall response rate of 28% (16 of 57). Stable disease of sufficient duration to be considered clinically meaningful (>10 weeks) was seen in an additional 15 dogs, for a resultant overall biological activity of 54% (31 of 57).

Conclusions: This study provides the first evidence that p.o. administered kinase inhibitors can exhibit activity against a variety of spontaneous malignancies. Given the similarities of canine and human cancers with regard to tumor biology and the presence of analogous RTK dysregulation, it is likely that such agents will demonstrate comparable antineoplastic activity in people.

Evaluation of 12- and 24-month survival rates after treatment with masitinib in dogs with nonresectable mast cell tumors

Kevin A. Hahn, DVM, PhD; Alfred M. Legendre, DVM, MS; Neil G. Shaw, DVM; Brenda Phillips, DVM; Gregory K. Ogilvie, DVM; Deborah M. Prescott, DVM, PhD; Stephen W. Atwater, DVM, MS; Janet K. Carreras, DVM; Susan E. Lana, DVM, MS; Tracy Ladue, DVM, MS; Anthony Rusk, DVM; Jean Pierre Kinet, MD; Patrice Dubreuil, PhD; Alain Moussy, MBA; Olivier Hermine, MD, PhD

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From the Department of Soft Tissue Pathology, Armed Forces Institute of Pathology, Washington, DC.

Prognostic and predictive significance of KIT protein expression and *c-kit* gene mutation in canine cutaneous mast cell tumours: A consensus of the Oncology-Pathology Working Group

Douglas H. Thamm[1] | Anne C. Avery[1] | Davide Berlato[2] | Julie Bulman-Fleming[3] | Craig A. Clifford[4] | A. Elizabeth Hershey[5] | Joanne L. Intile[6] | Pamela D. Jones[7] | Debra A. Kamstock[8] | Julius M. Liptak[9] | Alana Pavuk[10] | John Peauroi[11] | Roger Powell[12] | Kerry Rissetto[13] | Victor E. O. Valli[11] | Joshua D. Webster[14]

Masitinib is Safe and Effective for the Treatment of Canine Mast Cell Tumors

K.A. Hahn, G. Oglivie, T. Rusk, P. Devauchelle, A. Leblanc, A. Legendre, B. Powers, P.S. Leventhal, J.-P. Kinet, F. Palmerini, P. Dubreuil, A. Moussy, and O. Hermine

Background: Activation of the KIT receptor tyrosine kinase is associated with the development of canine mast cell tumors (MCT).

Hypothesis/Objective: To evaluate the efficacy of masitinib, a potent and selective inhibitor of KIT, in the treatment of canine MCT.

Animals: Two hundred and two client-owned dogs with nonmetastatic recurrent or nonresectable grade II or III MCT.

Methods: Double-blind, randomized, placebo-controlled phase III clinical trial. Dogs were administered masitinib (12.5 mg/kg/d PO) or a placebo. Time-to-tumor progression (TTP), overall survival, objective response at 6 months, and toxicity were assessed.

Resulsts: Masitinib increased overall TTP compared with placebo from 75 to 118 days ($P = .038$). This effect was more pronounced when masitinib was used as first-line therapy, with an increase in the median TTP from 75 to 253 days ($P = .001$) and regardless of whether the tumors expressed mutant (83 versus not reached [$P = .009$]) or wild-type KIT (66 versus 253 [$P = .008$]). Masitinib was generally well tolerated, with mild (grade I) or moderate (grade II) diarrhea or vomiting as the most common adverse events.

Conclusions and Clinical Importance: Masitinib is safe and effective at delaying tumor progression in dogs presenting with recurrent or nonresectable grade II or III nonmetastatic MCT.

Key words: Dog; KIT; Mast cell tumor.

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Pulse-Administered Toceranib Phosphate Plus Lomustine for Treatment of Unresectable Mast Cell Tumors in Dogs

J.H. Burton, R.O. Venable, D.M. Vail, L.E. Williams, C.A. Clifford, S.M. Axiak-Bechtel, A.C. Avery, and D.H. Thamm

Background: Nonresectable mast cell tumors (MCT) in dogs remain a therapeutic challenge, and investigation of novel combination therapies is warranted. Intermittent administration of tyrosine kinase inhibitors (TKI) combined with cytotoxic chemotherapy may effectively chemosensitize canine MCT while decreasing cost and adverse effects associated with either agent administered as monotherapy.

Hypothesis/Objectives: The primary study objectives were to (1) identify the maximally tolerated dose (MTD), (2) determine the objective response rate (ORR) and (3) describe the adverse event profile of pulse-administered toceranib phosphate (TOC) combined with lomustine.

Animals: Forty-seven client-owned dogs with measurable MCT.

Methods: Toceranib phosphate was given PO on days 1, 3 and 5 of a 21-day cycle at a target dosage of 2.75 mg/kg. Lomustine was given PO on day 3 of each cycle at a starting dosage of 50 mg/m^2. All dogs were concurrently treated with diphenhydramine, omeprazole, and prednisone.

Results: The MTD of lomustine was established at 50 mg/m^2 when combined with pulse-administered TOC; the dose-limiting toxicity was neutropenia. Forty-one dogs treated at the MTD were evaluable for outcome assessment. The ORR was 46% (4 complete response, 15 partial response) and the overall median progression-free survival (PFS) was 53 days (1 to >752 days). On multivariate analysis, variables significantly associated with improved PFS included response to treatment, absence of metastasis, and no previous chemotherapy.

Conclusions and clinical importance: Combined treatment with pulse-administered TOC and lomustine generally is well tolerated and may be a reasonable treatment option for dogs with unresectable or metastatic MCT.

Key words: Cancer; Chemotherapy; Dog; Tyrosine kinase inhibitor.

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Isotani M[1], Ishida N, Tominaga M, Tamura K, Yagihara H, Ochi S, Kato R, Kobayashi T, Fujita M, Fujino Y, Setoguchi A, Ono K, Washizu T, Bonkobara M.

Author information

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ORIGINAL RESEARCH

Cyclooxygenase inhibitors potentiate receptor tyrosine kinase therapies in bladder cancer cells in vitro

Masitinib monotherapy in canine epitheliotropic lymphoma.

Holtermann N[1], Kiupel M[2], Kessler M[3], Teske E[4], Betz D[5], Hirschberger J[1].

Author information

Abstract

This study evaluated efficacy and side effects of masitinib in canine epitheliotropic lymphoma. Complete remission occurred in 2 of 10 dogs and lasted for median 85 days. Five dogs went into partial remission for median 60.5 days. Three pretreated dogs did not respond to therapy. Side effects occurred in six dogs and were mostly mild to moderate. Immunohistochemistry was available for eight dogs. KIT receptor was negative in all of them, six of eight lymphomas stained strongly positive for stem cell factor (SCF). platelet-derived growth factor (PDGF)-AA was weakly positive in two and negative in six. PDGF-BB was negative in four tumours, weakly positive in one and strongly positive in three. One was strongly positive for PDGF receptor (PDGFR)-β, seven were negative for that receptor. Five showed strong expression of PDGFR-α, two showed weak expression, one was negative. In conclusion, masitinib is effective in treating canine epitheliotropic lymphoma. But its effects are most likely not generated through the KIT receptor.

Large granular lymphoma in six cats.

Sapierzyński R, Jankowska U, Jagielski D, Kliczkowska-Klarowicz K.

Abstract

Large granular lymphomas (LGLs) comprise a specific group of lymphomas regardless of classifi- cation scheme. An LGL consists of cells that show less or more mature morphology, but typically neoplastic cells possess cytoplasmic azurophilic granules clearly visible during cytological examin- ation. The aim of the present study was to present clinical and cytological data on large granular lymphomas in cats and to analyses the therapeutic responses in treated cases. During the period from 2012 to 2014 six cats were as having large granular lymphoma. In one cat a nasal form of LGL was recognized, a systemic form was recognized in another cat, and in four cases an alimentary form was recognized. Cellular samples for cytopathology were collected from the cat with nasal cavity mass, from the enlarged mandibular lymph node and thoracic cavity from second cat, and in four cats from the abdominal mass during ultrasound-assisted fine-needle biopsy. Therapy was introduced in 5 of the 6 cats. In two cases palliative therapy with glucocorticoids was conducted, in two cases chemotherapy with COP protocol, and therapy with masitinib in one case. The median of survival time for cats treated with anticancer therapy was 9 months, the median of survival time for cats treated with glucocorticoids was 1.5 months. In conclusion, large granular lymphomas, especially the alimentary form, are a relatively common type of lymphoma in cats. Simple diagnostic methods such as clinical examination, imaging techniques and routine cytology are sufficient in majority of cases. Despite aggressive behavior and poor general prognosis, conventional chemotherapy lead to a good response in some treated cats regardless of anatomic form and histologic grade of malignancy.

CHIC2 deletion, a surrogate for FIP1L1-PDGFRA fusion, occurs in systemic mastocytosis associated with eosinophilia and predicts response to imatinib mesylate therapy.

Pardanani A[1], Ketterling RP, Brockman SR, Flynn HC, Paternoster SF, Shearer BM, Reeder TL, Li CY, Cross NC, Cools J, Gilliland DG, Dewald GW, Tefferi A.

Author information

Abstract

Imatinib mesylate is effective in the treatment of hematologic malignancies that are characterized by either abl- or PDGFR beta-activating mutations. The drug is also active in a subset of patients with eosinophilic disorders and systemic mast cell disease (SMCD). Recently, a novel tyrosine kinase that is generated from fusion of the Fip1-like 1 (FIP1L1) and PDGFR alpha (PDGFRA) genes has been identified as a therapeutic target for imatinib mesylate in hypereosinophilic syndrome (HES). We used fluorescence in situ hybridization (FISH) to detect deletion of the CHIC2 locus at 4q12 as a surrogate for the FIP1L1-PDGFRA fusion. CHIC2 deletion was observed in bone marrow cells for 3 of 5 patients with SMCD associated with eosinophilia. Deletion of this locus and expression of the FIP1L1-platelet-derived growth factor receptor alpha (PDGFRA) fusion was also documented in enriched eosinophils, neutrophils, or mononuclear cells by both FISH and reverse transcriptase-polymerase chain reaction (RT-PCR) for one patient. While all 3 patients with the FIP1L1-PDGFRA rearrangement achieved a sustained complete response with imatinib mesylate therapy, the other two, both carrying the c-kit Asp816 to Val (Asp816Val) mutation, did not. These observations suggest that the FIP1L1-PDGFRA rearrangement occurs in an early hematopoietic progenitor and suggests that the molecular pathogenesis for a subset of SMCD patients is similar to that of HES. Screening for the FIP1L1-PDGFRA rearrangement and Asp816Val mutation will advance rational therapy decisions in SMCD.

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Спасибо за внимание

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