Vemurafenib (PLX4032): An Orally Available Inhibitor of Mutated BRAF for the Treatment of Metastatic Melanoma

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OBJECTIVE: To summarize the preclinical and clinical data on vemurafenib, approved by the Food and Drug Administration (FDA) on August 17, 2011, and discuss the drug's clinical advantages and limitations.

DATA SOURCES: An English-language literature search of MEDLINE/PubMed (1966-August 2011), using the terms PLX4032, RG7204, RO5185426, vemurafenib, and metastatic melanoma, was conducted. In addition, information and data were obtained from meeting abstracts, clinical trial registries, and news releases from the FDA.

STUDY SELECTION AND DATA EXTRACTION: All relevant published articles and abstracts on vemurafenib were included. Clinical trial registries and meeting abstracts were used to obtain information regarding ongoing trials. All peer-reviewed articles containing information regarding the clinical safety and efficacy of vemurafenib were evaluated for inclusion.

DATA SYNTHESIS: Before the recent approval (March 2011) of ipilimumab, there was no first-line standard-of-care therapy, with proven overall survival benefit, for the treatment of malignant metastatic melanoma. Unlike ipilimumab, which acts through immune-modulation, vemurafenib is a novel, molecularly targeted therapeutic with preferential efficacy toward a specific mutated oncogenic BRAF-signaling mediator. In recently published results of a Phase 3 clinical trial comparing dacarbazine with vemurafenib, vemurafenib prolonged progression-free and overall survival, with confirmed objective response rate of 48% (95% CI 42 to 55) versus 5% (95% CI 3 to 9) for patients who received dacarbazine ($p < 0.001$).

CONCLUSIONS: Vemurafenib offers a novel, first-line, personalized therapy for patients who have mutated BRAF. Clinical trials of vemurafenib in combination with ipilimumab or other targeted or cytotoxic chemotherapeutic agents may provide more effective regimens with long-term clinical benefit.

KEY WORDS: melanoma, PLX4032, RG7204, RO5185426, vemurafenib.

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Advanced metastatic melanoma is responsible for 80% of overall deaths caused by skin cancers.[1,2] In the US, melanoma is the fifth most common type of new cancer diagnosis in men, and the seventh in women.[3] Whites are 30 times more likely to develop melanoma than are African Americans. It is estimated that, in 2011, 70,230 new melanomas will be diagnosed and about 8790 people in the US will die of melanoma. Unlike other types of cancer, melanoma affects younger as well as older people, with a wide range of age distribution.[3] The response rate for therapies approved by the Food and Drug Administration (FDA), dacarbazine and high-dose interleukin 2, ranges from 10% to 20%, with no significant improvement in overall or progression-free survival.[1] In March 2011, the FDA approved ipilimumab, a human monoclonal antibody that potentiates T-cell response by blocking cytotoxic T-lymphocyte–associated antigen, to treat advanced metastatic melanoma.[4] In clinical trials, the median overall survival rate of patients treated with ipilimumab, with or without glycoprotein 100 (gp100), a peptide vaccine, was approximately 10 months, while patients treated with gp100 alone had a 6.4-month overall survival rate ($p < 0.003$).[4] More recently, ipilimumab in combination with dacarbazine resulted in improvement of overall survival compared with dacarbazine alone (11.2 months vs 9.1 months; $p < 0.001$).[5] Because of the immune-based mechanism of action of ipilimumab, 38.1% of patients treated with ipilimumab plus dacarbazine had severe immune-related adverse events, compared with 4.4% of patients treated with dacarbazine.[5]

Progress in understanding the genetic basis of cancer, facilitated by rapid advances in high-throughput genome-scale technologies, has opened the door for the development of molecularly targeted therapeutics that preferentially affect malignant cells.[6] A well-established signaling pathway that mediates the growth signals that drive cancer development and progression is the RAS-RAF-MEK-ERK mitogen-acti-

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vated protein (MAP) kinase cascade (Figure 1).[7] Attempts to directly inhibit RAS, which is mutated to an oncogene in approximately 30% of human cancers, have largely been unsuccessful.[8] Therefore, ongoing efforts are focused on targeting the RAS downstream-effector pathways, such as the MAP kinase signaling cascades.[8]

Three genes encode for the RAF serine/threonine kinases (BRAF, CRAF, and ARAF), which are regulated by interaction with RAS.[8,9] Activating somatic missense mutations in BRAF are present in several types of human cancers, such as melanoma, thyroid, colorectal, and ovarian.[10,11] The most predominant mutation is 1799T>A, which causes a single substitution of valine 600 to glutamic acid in the activating region of the kinase domain.[9] The kinase activity of BRAF V600E is elevated relative to BRAF wild type, leading to constitutive phosphorylation of downstream ERK.[12] In melanoma, BRAF is mutated in approximately 30-70% of patients. BRAF V600E represents 74-90% of these mutations.[9] It has been postulated that selective targeting of the mutated BRAF may offer an opportunity to develop a highly selective therapeutic approach, with minimal undesired effects on nonmalignant cells.

Vemurafenib (Zelboraf), which was co-developed by Plexxikon and Hoffmann-La Roche/Genentech,[13] is an orally available BRAF inhibitor that selectively targets the mutated BRAF V600E isoform.[14] Vemurafenib was approved by the FDA on August 17, 2011, as a first-line single-agent therapy for the treatment of BRAF V600E–positive malignant melanoma as detected by an FDA-approved test.[15] A companion diagnostic test, the cobas 4800 BRAF V600 Mutation Test, developed and manufactured by Roche Molecular Systems (Roche Diagnostics, Pleasanton, CA), was simultaneously approved to test whether a patient's melanoma is BRAF V600E–positive.[15]

Data Sources

An English-language literature search of PubMed was performed between April 15, 2011, and August 23, 2011, using the terms vemurafenib, PLX4032, RG7204, RO5185426, and metastatic melanoma. Additional information was obtained from clinical trial registries, FDA news releases, and meeting abstracts of the American Society of Clinical Oncology (www.asco.org/ascov2/meetings/abstracts). All peer-reviewed articles containing clinically relevant information were evaluated for inclusion. Information regarding the cost of vemurafenib and the companion genetic test was obtained from the medpage TODAY Web site (www.medpagetoday.com).

Pharmacology

Protein kinases catalyze the phosphorylation of serine, threonine, or tyrosine residues to regulate signal transduction pathways involved in a wide variety of cellular functions, such as proliferation and cell death.[16] Vemurafenib is an adenosine triphosphate (ATP)–competitive inhibitor, highly selective for mutant BRAF V600E.[17] In preclinical in vitro and in vivo models of melanoma, vemurafenib preferentially inhibited mutated BRAF (50% inhibitory concentration [IC50] 31 nM), relative to wild-type BRAF (IC50 100 nM) and CRAF (IC50 48 nM), which led to cell cycle arrest and induction of apoptosis exclusively in cell lines harboring either homozygous or heterozygous BRAF V600E.[13] The functional selectivity toward mutated BRAF over the wild-type form could be attributed to the protein structural confirmation, which is locked into an active kinase state, causing the ATP binding site to be readily accessible.[18] Inhibition of downstream ERK phosphorylation and cellular proliferation was detectable following vemurafenib treatment.[13]

Clinical Trials

PHASE 1 DOSE-ESCALATION TRIAL

The primary goal of this study was to identify the maximum tolerated dose to be used for a Phase 2 trial and evaluate the safety and pharmacokinetic parameters following continuous vemurafenib twice-daily administration.[14] The recommended Phase 2 dose was defined as the highest dose at which no more than 1 of 6 patients presented with dose-limiting adverse events. Because of the low bioavailability of the original crystalline formulation, the study was

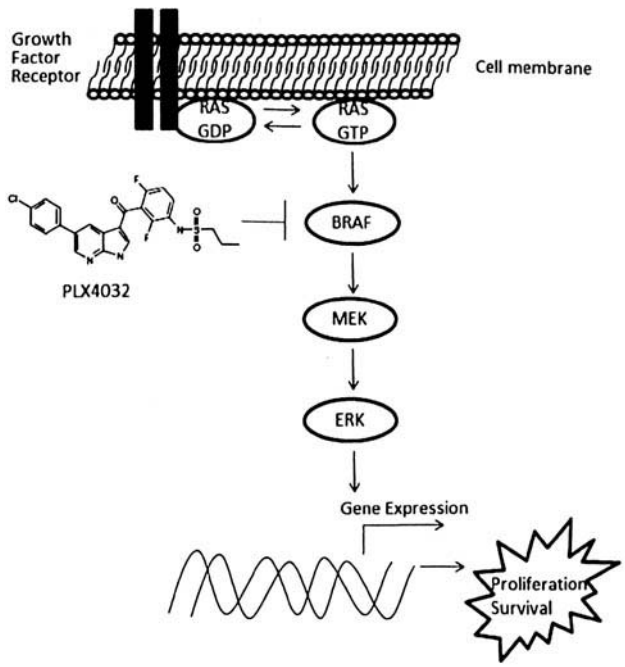

Figure 1. The mitogen-activated protein (MAP) kinase pathway. Growth factor stimulation signals through the oncogenic RAS, which activates the MAP kinase pathway, leading to cellular proliferation and survival. Vemurafenib (PLX4032) disrupts MAP kinase signaling through selective inhibition of mutated BRAF.[7]

temporarily halted so that the drug could be reformulated. Several groups of 3-6 patients received escalating doses of vemurafenib in the form of capsules of highly bioavailable micro-precipitated bulk powder. The dose started at 160 mg twice daily and was escalated to 240 mg, then 320 or 360 mg, 720 mg, and finally 1120 mg twice daily. Patients were monitored for at least 4 weeks for any adverse events before they received higher doses. Therapy was interrupted only if dose-limiting adverse events were observed or the disease progressed. The dose-escalation phase was open to patients with any type of tumor, regardless of the BRAF mutation status, but the cohort was enriched with patients who had BRAF V600E melanomas. All patients had tumors that did not respond to standard therapy, and their life expectancy was at least 3 months. Patients with active central nervous system metastasis were excluded. Because of the development of cutaneous squamous-cell carcinoma (CSCC) during the trial, the protocol was amended to include dermatologic evaluation at baseline and every 2 months during the study. To assess tumor response, computed tomographic scans were performed in all patients and patient responses were evaluated based on Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0.[14,19] Disappearance of all target lesions was considered a complete response, while a decrease by at least 30% in the sum of the largest diameter of each target lesion, relative to the corresponding sum at baseline, was considered a partial response.[14]

A total of 55 patients, divided into groups of 3-6 patients, were enrolled in the dose-escalation phase. An additional 32 patients with BRAF V600E metastatic melanoma were enrolled in the extension phase. Dose-limiting adverse events were initially observed at 720 mg twice daily; 1 of 7 patients had grade 2 rash, nausea, and photosensitivity. The next highest dose, 1120 mg twice daily, caused dose-limiting adverse events in 4 of 6 patients; therefore, an intermediate dose of 960 mg twice daily was evaluated and found to be tolerated by a group of 6 patients. Based on these results, the Phase 2 recommended dose was 960 mg twice daily. Analysis of complete and partial tumor response revealed a dose-response relationship. Complete or partial tumor response was observed in 1 of the 16 patients who received 240 mg twice daily. Two of the 4 patients who received 320 mg twice daily had complete or partial response. At 720 mg twice daily, 4 of 6 patients had tumor response, as did 4 of 5 patients at 1120 mg twice daily. Tumor response was detectable at all metastatic sites, including the bone, small bowel, and liver. Interestingly, 5 patients with non-BRAF V600E melanoma who received doses of 240 mg or higher twice daily had no tumor response, suggesting that vemurafenib is selective for BRAF V600E–positive melanomas.[14]

Following the dose-escalation study, 32 additional patients with BRAF V600E–positive melanoma were enrolled in the extension cohort study. All patients received vemurafenib 960 mg twice daily. Positive tumor response in the form of shrinkage was observed in 26 of 32 patients (81%, best overall response rate), with 2 complete and 24 partial responses. At the time of publication of the results, 16 of the 32 patients were still in the study. The complete or partial responses lasted from 2 to more than 18 months, with median progression-free survival of more than 7 months.[14]

Pharmacokinetics

Pharmacokinetic assessment was performed during the escalation trial. Plasma samples were collected at days 1 and 15 during the first 4 weeks of treatment and then every 4 weeks. At the recommended Phase 2 dose of 960 mg twice daily, the mean (SD) area under the plasma concentration time curve (AUC) over a 24-hour period ($AUC_{0\text{-}24}$) was 1741 (639) μM × hour. The mean maximum steady-state concentration was 86 (32) μM and the mean half-life was approximately 50 hours, suggesting that drug exposure at steady-state was consistent.[14] An ongoing clinical trial (NCT01264380) is evaluating the effect of food on the pharmacokinetics of single-dose vemurafenib in patients with BRAF V600E mutation-positive metastatic melanoma.[20] Another ongoing, multicenter, open-label study (NCT01001299) is investigating the pharmacokinetic interaction of vemurafenib with a cocktail of caffeine, warfarin, vitamin K, omeprazole, dextromethorphan, and midazolam to probe for CYP450-dependent metabolism.[21]

Pharmacodynamics

At the recommended Phase 2 dose, the levels of biomarkers downstream of BRAF, phosphorylated ERK, cyclin D1, and the proliferation marker Ki-67, were significantly reduced at day 15 of the treatment, relative to pretreatment levels, suggesting that vemurafenib efficiently inhibited the MAP kinase pathway. In addition, results from positron-emission tomography, which assesses 18F-fluorodeoxyglucose (FDG) uptake, at baseline and day 15 of treatment showed significant reduction in FDG uptake in all patients. Collectively, the results indicated that vemurafenib achieved its predicted pharmacodynamic effects.[14]

PHASE 2 TRIAL

Vemurafenib was evaluated in an open-label multicenter study in previously treated patients with BRAF V600E metastatic melanoma.[22] The primary endpoint was best overall response rate, with a target of 30%. A total of 132 patients were enrolled in the study. Patients' best overall response rate was 52.3% (95% CI 43 to 61). The median progression-free survival was 6.2 months (95% CI 5.6 to 6.8). The most common adverse events, detected in more than 25% of the patients, were grade 1-2 arthralgia, rash, photosensitivity, fatigue, alopecia, pruritus, and skin papilloma. About 24% of the patients developed CSCC.

PHASE 3 TRIAL

Most recently, the results of a Phase 3 trial providing the first survival data for vemurafenib were published.[23] A large multicenter Phase 3 clinical study (675 patients enrolled through 100 sites worldwide) was conducted to assess the effect of vemurafenib compared with dacarbazine on overall and progression-free survival. All patients had unresectable, previously untreated, advanced BRAF V600E–positive melanoma (stage IIIC or IV). Retrospective analysis by Sanger sequencing identified 20 patients with no BRAF V600E mutation. Tumor responses were evaluated at baseline, weeks 2 and 12, and then every 9 weeks, according to RECIST version 1.1.[24] This updated version of RECIST 1.0 is more suitable for assessment of randomized Phase 3 trials, in which progression-free survival is the primary endpoint. Based on the results of Phase 1 and Phase 2 trials, the coprimary endpoints for the vemurafenib Phase 3 study were overall and progression-free survival.[23]

Secondary endpoints included response rate, response duration, and safety. Survival criteria were defined as the time from randomization to death from any cause. Progression-free survival was defined as the time from randomization to documented disease progression or death. The study participants were randomized to receive either vemurafenib 960 mg orally twice daily or dacarbazine 1000 mg/m^2 intravenously every 3 weeks. Treatment doses were reduced for both vemurafenib and dacarbazine when grade 2 adverse events or worse were reported.[23]

Vemurafenib treatment was discontinued until the toxic effects were resolved to grade 1 and then resumed at 720 mg twice daily. In case of recurrence of grade 2 toxicity, the dose was reduced to 480 mg twice daily, and if there was no improvement, treatment was discontinued. Dacarbazine treatment was interrupted when grade 3 or 4 toxicity occurred and resumed within a week at full dose after resolution to grade 1 or reduced to 75% of the dose in case of grade 2 toxicity. Treatment with vemurafenib or dacarbazine was discontinued upon disease progression.[23]

The results of the Phase 3 trial corroborated the preliminary efficacy data reported in Phase 1 and Phase 2 trials. Vemurafenib treatment reduced the risk of death by 63%.[23] The hazard ratio for death in the vemurafenib group was 0.37 (95% CI 0.26 to 0.55; $p < 0.001$). The 6-month overall survival rate for the vemurafenib group was 84% (95% CI 78 to 89) and 64% for the dacarbazine group (95% CI 56 to 73). Vemurafenib reduced the risk of tumor progression by 74%.The hazard ratio for tumor progression for the vemurafenib arm was 0.26 (95% CI 0.20 to 0.33; $p < 0.001$). The median progression-free survival was 5.3 months for the vemurafenib group and 1.6 months for the dacarbazine group ($p < 0.001$). In the vemurafenib group, 48% of the patients (106/219; 95% CI 42 to 55) had a confirmed objective response, with 104 patients having a partial response and 2 patients having a complete response. The median time to response was 1.45 months. Very few patients in the dacarbazine group had detectable decrease in tumor size, with only 12 of 220 patients (5%; 95% CI 3 to 9) having a partial response; the median time to response was 2.7 months. The difference in tumor response between the 2 groups was highly significant ($p < 0.001$).[23]

Resistance to Vemurafenib

Despite the initial response to vemurafenib treatment, acquired resistance eventually developed, and patients relapsed.[14,22,23] The reported duration of median progression-free survival from the Phase 3 clinical trial was 5.3 months.[23] Resistance to kinase inhibitors is well documented in other malignancies, such as chronic myelogenous leukemia (CML).[25] In most resistance events, a secondary mutation in the target kinase domain develops and prevents the binding of the kinase inhibitor. The discovery of this mechanism in CML led to the development of second-generation inhibitors such as dasatinib and nilotinib. Early preclinical studies on vemurafenib resistance unexpectedly revealed possible distinct resistance mechanisms that did not involve secondary mutations in the kinase catalytic domains.[26-28] A clinical case study based on analysis of 138 cancer genes in a tumor sample obtained from a patient with melanoma relapse revealed an activating mutation at codon 121 in MEK1, which was absent in the pretreatment tumor tissue.[29] An ongoing clinical trial is evaluating the use of a combination of a similar mutant BRAF oral inhibitor, GSK2118436, and an oral MEK 1/2 GSK1120212 as a possible clinical strategy to overcome acquired resistance following mutant BRAF inhibition.[30]

All of the reported preclinical studies suggested that malignant cells reactivate alternative oncogenic pathways following mutant BRAF inhibition.[26-28] Therefore, alternative therapeutic combination regimens could be devised based on understanding these molecular mechanisms.[31] Besides the observed acquired resistance, about 20% of patients with BRAF V600E mutation in Phase 1 trials were intrinsically resistant to vemurafenib.[14] A recent preclinical study suggested the involvement of an alternative oncogenic PI3/AKT pathway in intrinsic vemurafenib resistance.[32] If these preclinical findings are proven to be clinically relevant, combined inhibition of both the BRAF-mutated MAP kinase and AKT pathways may offer an alternative therapeutic approach for this subset of intrinsically resistant patients.

Adverse Effects

Malignant-cell survival is highly dependent on specific, constitutively active kinase-mediated signaling pathways.[16] Targeting altered promitogenic or prosurvival kinases for cancer therapy might be associated with less incidence of adverse effects known to be associated with conventional glob-

al cytotoxic agents, which affect rapidly dividing cells indiscriminately.[33] However, because of long-term disruption of key signaling pathways, molecularly targeted therapies may cause distinct toxicities.[33] Table 1 summarizes grade 2 or higher adverse effects associated with vemurafenib 960 mg twice daily.[14,23] In the Phase 1 extension study, 13 of 32 patients (41%) needed dose reduction to 720 mg twice daily in 10 patients, 600 mg twice daily in 1 patient, and 480 mg twice daily in 2 patients.[14] In the Phase 3 study, adverse events caused a dose modification or treatment interruption in 129 of 336 patients (38%).[23] Interestingly, 31% of patients in the extension cohort and 15% in the dose-escalation cohort developed CSCC within 8 weeks of treatment initiation.[14] These lesions were also seen in Phase 2 and 3 trials (approximately 20% of patients), and they were completely resected with no further complications.[22,23] Potent BRAF inhibition could be a predisposing factor for CSCC development. Several cases of CSCC were associated with the multikinase pan-RAF inhibitor sorafenib, but to a lesser extent.[34,35] Similar observations were reported during the early clinical studies of GSK2118436, another selective potent inhibitor of mutated BRAF.[36] The detailed in vivo mechanism(s) involved in the development of these lesions remains unknown.

Discussion

The relative success of vemurafenib in the treatment of BRAF V600E–positive metastatic melanoma was dampened by acquired resistance caused by diverse molecular mechanisms. Chronic administration of vemurafenib may cause additional toxicities that remain to be evaluated.[37] It is anticipated that vemurafenib will be studied in combination with other therapies, such as dacarbazine or the recently approved ipilimumab.[18] The results of these studies may provide alternative therapeutic regimens for patients with melanoma. In addition, an ongoing, open-label, single-arm, Phase 2, multicenter study is evaluating vemurafenib for the treatment of metastatic melanoma in patients with brain metastasis (NCT01378975).[38] Early results suggest possible efficacy in reducing the burden of brain metastatic lesions.[39]

The cost of cancer care in the US continues to escalate, possibly because of the growing, chronic use of expensive, molecularly targeted therapies.[40] The predicted cost of vemurafenib is $9400 per month, and the companion genetic mutation test will cost $120-$150.[41] Pharmacoeconomic studies will be needed to assess the cost-effectiveness of vemurafenib treatment.

Overall costs associated with the use of molecularly targeted therapies could be reduced through identification of biomarkers for prospective patient selection.[42] For example, patients with colorectal cancer with KRAS mutation do not respond to the epidermal growth factor receptor inhibitor cetuximab.[43] The incremental cost-effectiveness ratios are lower for patients with wild-type KRAS tumors.[42] In addition to drug direct-related costs, patient monitoring costs should be taken into consideration.[44] Since vemurafenib resistance mechanisms could be patient-specific, genomic analysis might be needed to identify the most suitable salvage combi-

Table 1. Adverse Effects in More Than 5% of Patients Receiving Vemurafenib[a]

Adverse Event, n (%)	Extension Phase[14] (n = 32)	Phase 3 Study[22] (n = 336)
Arthralgia		
grade 2	10 (31)	60 (18)
grade 3	1 (3)	11 (3)
Rash		
grade 2	7 (22)	33 (10)
grade 3	1 (3)	28 (8)
Squamous-cell carcinoma		
grade 3	NA	40 (12)
Keratoacanthoma		
grade 2	0	7 (2)
grade 3	10 (31)	20 (6)
Nausea		
grade 2	4 (12)	25 (7)
grade 3	1 (3)	4 (1)
Fatigue		
grade 2	2 (6)	38 (11)
grade 3	2 (6)	6 (2)
Alopecia		
grade 2	NA	26 (8)
Pruritus		
grade 2	4 (12)	19 (6)
grade 3	0	5 (1)
Hyperkeratosis		
grade 2	NA	17 (5)
grade 3	NA	4 (1)
Diarrhea		
grade 2	NA	16 (5)
grade 3	NA	2 (<1)
Headache		
grade 2	NA	15 (4)
grade 3	NA	2 (<1)
Vomiting		
grade 2	NA	9 (3)
grade 3	NA	4 (1)
Lymphopenia		
grade 2	2(6)	NA
grade 3	0	NA
Neutropenia		
grade 2	NA	1 (<1)
grade 3	NA	0
grade 4	NA	1 (<1)
grade 5	NA	0

NA = not available.
[a]Dose used was 960 mg twice daily.

nation regimen.[44] Unfortunately, several hurdles are still facing the field of biomarker development; mainly, inadequate reimbursement of biomarker tests by Medicare and private insurance companies.[44] Additional pharmacoeconomic studies are needed to establish the validity of the overall cost benefit of integrating biomarker tests with the use of molecularly targeted therapeutics.

Summary

The field of personalized cancer therapeutics will continue to make strides toward improved patient care; however, more challenges are expected. Phase 3 trial results corroborate the clinical efficacy of vemurafenib as a first-line therapeutic agent for the treatment of advanced BRAF V600E– positive metastatic melanoma.[23] Further research efforts to better understand the molecular mechanism(s) responsible for acquired drug resistance may identify next-generation therapies that target mutated promitogenic and prosurvival kinases.

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Vemurafenib (PLX4032): Un Inhibidor de BRAF Mutado Disponible por vía Oral Para el Tratamiento del Melanoma Metastático

Y Heakal, M Kester, y S Savage

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EXTRACTO

OBJETIVO: Resumir los datos preclínicos y clínicos del fármaco vemurafenib y discutir sus ventajas y limitaciones clínicas.

FUENTES DE INFORMACIÓN: Se realizó una búsqueda bibliográfica de la literatura en lengua inglesa mediante la base de datos MEDLINE/PUBMED (1966-agosto 2011) con los términos de búsqueda PLX4032, RG7204, RO5185426, vemurafenib, y metastatic melanoma (melanoma metastático). Además, se obtuvo información y datos de los extractos de congresos, registros de ensayos clínicos y comunicados de la FDA.

SELECCIÓN DE FUENTES DE INFORMACIÓN Y MÉTODO DE EXTRACCIÓN DE INFORMACIÓN: Se incluyeron todos los artículos y extractos publicados relevantes sobre vemurafenib. Los registros de ensayos clínicos y los extractos de congresos se emplearon para obtener información sobre los ensayos clínicos en curso. Se evaluaron para su inclusión todos los artículos de revisión por pares que contenían información sobre la seguridad y eficacia clínica de vemurafenib.

SÍNTESIS: Antes de la aprobación reciente de ipilimumab en marzo de 2011, no había un régimen estándar de primera línea, con beneficios probados sobre la supervivencia general, para el tratamiento del melanoma metastático maligno. A diferencia de ipilimumab, que actúa mediante la modulación inmune, vemurafenib es un agente terapéutico novedoso dirigido a la molécula con eficacia preferente hacia un mediador específico de señalización de la mutación oncogénica en el gen BRAF. En el ensayo clínico de fase 3 publicado recientemente, vemurafenib prolongó la supervivencia libre de progresión y general en comparación con dacarbazina, con una tasa de respuesta objetiva confirmada del 48% (IC 95% 42 a 55) frente al 5% (IC 95% 3 a 9) para pacientes tratados con dacarbazina ($p < 0.001$).

CONCLUSIONES: Debido a la falta de modalidades de tratamiento efectivo para el melanoma metastático avanzado, la aprobación reciente de vemurafenib por parte de la FDA ofrece una terapia novedosa y personalizada de primera línea para pacientes con BRAF mutado. Además, ensayos clínicos futuros de vemurafenib en combinación con ipilimumab u otros agentes quimioterapéuticos dirigidos o citotóxicos, pueden proporcionar más regímenes efectivos con beneficio clínico a largo plazo.

Traducido por Enrique Muñoz Soler

Vemurafenib (PLX4032): Un Inhibiteur par Voie Orale du BRAF Muté Dans le Traitement du Mélanome Métastatique

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RÉSUMÉ

OBJECTIFS: Résumer les données cliniques et précliniques sur le vemurafenib et discuter de ses avantages cliniques et de ses limites.

SOURCES DE L'INFORMATION: La littérature de langue anglaise a été fouillée à l'aide de MEDLINE/PubMed (1966-août 2011) en utilisant les mots clés: PLX4032, RG7204, RO5185426, vemurafenib et metastatic melanoma. De plus, des données et des informations ont été obtenues à partir d'abrégés de congrès, de registres d'études cliniques, et des nouvelles émises par la FDA.

SÉLECTION DES ÉTUDES ET EXTRACTION DE L'INFORMATION: Tous les articles et les abrégés pertinents et publiés sur le vemurafenib ont été inclus. Les registres des études cliniques et les abrégés de congrès ont été utilisés pour obtenir des informations concernant les études en cours. Tous les articles comportant une révision par les pairs, et contenant des informations sur l'efficacité et la sécurité clinique du vemurafenib ont été évalués pour inclusion.

SYNTHÈSE DE L'INFORMATION: Avant la récente approbation de l'ipilimumab en mars 2011, il n'y avait pas de traitement de première ligne considéré comme un standard de soins démontrant un bénéfice global de survie pour le traitement du mélanome métastatique malin. A la différence de l'ipilimumab qui agit en modulant le système immunitaire, le vemurafenib est une nouvelle thérapie moléculaire avec une efficacité préférentielle sur un médiateur BRAF oncogénique muté. Dans les études récentes de phase 3, le vemurafenib a prolongé la période de survie sans progression et la survie globale en comparaison avec la dacarbazine, avec un taux de réponse confirmé de 48% (IC 95% 42 à 55) par rapport à 5% (IC 95% 3 à 9) pour les patients recevant la dacarbazine ($p < 0.001$).

CONCLUSIONS: En raison de l'absence de modalités thérapeutiques efficaces dans le traitement du mélanome métastatique avancé, l'approbation récente par la FDA du vemurafenib offre une nouvelle thérapie de première ligne personnalisée pour les patients qui portent le BRAF muté. De plus, les études cliniques à venir avec le vemurafenib en combinaison avec l'ipilimumab, ou d'autres chimiothérapies ciblées ou cytotoxiques, pourront supporter des régimes thérapeutiques plus efficaces avec des bénéfices cliniques à long terme.

Traduit par Marc Parent