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BRAF inhibitor :

The data we have are now insufficient to make recommendations about the concomitant use of BRAFi and radiotherapy

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Mechanisms of actions

BRAF is an integral part of the RAS-RAF-MEK-ERK (mitogen-activated protein kinase) signal transduction pathway, a protein kinase cascade which regulates cellular growth, proliferation, differentiation, and survival in response to extracellular signals, including growth factors, cytokines, and hormones .
Some mutations in the BRAF gene including V600E result in constitutively activated BRAF proteins, which can cause cell proliferation in the absence of growth factors that would normally be required for proliferation.
BRAF gene mutations are found in about 60% of melanona cells. The most common mutation in BRAF is caused by a single amino acid substitution of valine for glutamine at codon 600, representing the majority of BRAF mutations found in human cancer. (1)
Vemurafenib was the first selective BRAF inhibitor approved in advanced melanoma with BRAF V600 mutation (2), followed by Dabrafenib, a potent and reversible ATP-competitive inhibitor that selectively inhibits the BRAF V600E kinase (3).

Potential interaction with radiotherapy

Inhibition of BRAF has been associated with radiosensitization in vitro.
Sambade et al (4) found that for V600E mutant melanoma cell lines, radiosensitization was due, in part, to alterations in the cell cycle distribution: Vemurafenib increased cell cycle arrest in G1 through inhibition of the MAPK/Erk signal transduction pathway. This suggests that PLX-4032 or other B-RAF inhibitors in combination with radiation could provide improved radio-therapeutic response in B-Raf mutant melanomas.

Preclinical data

Desgupta et al, have assessed the interaction between PLX4720, a specific BRAF V600 inhibitor and some human carcinoma cell lines (melanoma, colon and thyroid carcinoma) demonstrating additive activity between radiation and PLX4720. In cells with BRAF V600E mutations, PLX4720 caused cell cycle arrest at G1, and, when combined with radiation, caused a combined G1 and G2 cell cycle arrest; this pattern of cell cycle effects was not seen in the BRAF wild type cell line (5).
Hecht et al (6) evaluated radiosensitivities in 35 blood samples of melanoma patients with or without BRAF inhibition. Each blood sample was divided into two portions, one of which was irradiated with 2 Gy and the other was not. Chromosomal aberrations were then analyzed via three-color fluorescence in situ hybridization (FISH). Again, patients who were or had taken BRAFi demonstrated increased radiosensitivity. Interestingly, this increased effect was significantly associated with Vemurafenib but not with Dabrafenib.

Clinical data on activity

Interesting results, have been reported in 6 patients with unresectable melanoma disease, treated with induction vemurafenib and then receiving radiation therapy (median dose 57 Gy, conventional fractionation), with 3 patients receiving debulking interval surgery (7) With 29 months' follow-up, local control was 100%. The 3 patients who experienced relapse received salvage therapy to become free of disease at latest follow-up.

Lee and colleagues (8) reported a case report in which a patient with positive cerebral spinal fluid cytology developed after 4 months of vemurafenib, underwent to whole brain irradiation (30 Gy in 10 fr) with vemurafenib held 7 days before and after radiotherapy. With a follow up of 18 months after RT, the cerebral spinal fluid was still negative without skin or non-dermatitis skin toxicity. The authors hypothesized that RT could have altered the permeability of the blood brain barrier allowing greater absorption of the drug in the spinal fluid.

Baroudjian et al (9) reported a complete metabolic response in a patient who had progression in the axilla, after radiotherapy 30 Gy in 6 fractions with concomitant vemurafenib.

Summary on activity

The data we have are now insufficient to make recommendations about the concomitant use of BRAFi and radiotherapy.

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