CLINICAL TRIALS

NEW OPTIONS FOR MELANOMA?

The blood–brain barrier has long been a major obstacle in the systemic treatment of patients with brain metastases, who are often excluded from clinical trials. An example of this issue is patients with melanoma that has metastasized to the brain, these patients have a median overall survival of only 4–5 months, which is even shorter than the already poor survival for patients with advanced-stage melanoma without metastases (9–11 months). The advent of the BRAF-targeting agent vemurafenib has improved the treatment options for patients with BRAF-mutated melanoma, and now a second-generation BRAF-targeting agent, dabrafenib, has shown activity in early clinical trials including patients with brain metastases.

The phase I trial was led by Gerald Falchook and recruited 184 patients with solid tumours; 28 patients with solid tumours that were not melanoma and 156 patients with melanoma. The initial phase of the trial established the dose for future later-stage clinical trials as 150 mg of dabrafenib given twice daily. The most common grade 2 and above adverse events were cutaneous squamous-cell carcinoma or keratoacanthoma, fatigue and pyrexia.

After the dose for future trials had been determined, patients received this dose in the phase I trial and the researchers used this opportunity to get some preliminary indications of the efficacy of the agent. In total, 46 patients with BRAF-mutated melanoma received this dose of dabrafenib; 10 of these patients had untreated brain metastases. Of the patients with brain metastases, nine had a decrease in the size of the brain lesions, and four achieved a complete resolution of all brain lesions. All of these patients were alive 5 months into the follow-up period and one was still on study at 19 months.

More-extensive trials of dabrafenib are already underway. Falchook explains the promise of this agent: “dabrafenib is the first drug of its class to show activity in the treatment of melanoma brain metastases. Clinical trials of melanoma usually exclude patients with brain metastases ... we hope that the introduction of new drugs that are effective in BRAF-mutant melanoma metastasized to the brain will result in new trial designs that allow such patients to be included.”

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