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Letter to the Editor

The use of buparlisib as a radiosentisiser: What about toxicity?

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In a recent article, McGowan *et al.* reported on the first clinical trial using a phospoinositide 3-kinase (PI3K) inhibitor as a radiosentisizer in patients with non-small cell lung carcinoma [1]. Palliative thoracic radiotherapy (20 Gy in 5 fractions) was combined with buparlisib (a pan-class I PI3K inhibitor) at dose levels of 50 mg, 80 mg and 100 mg once daily. As no dose limiting toxicity was reported, 100 mg was considered to be the maximum tolerated dose. In a total of 21 treated patients (13 in the cohort with the highest dosage), three cases of grade III toxicity were seen which were regarded to be related to buparlisib: one patient with hypoalbuminaemia and two patients with extreme fatigue. In addition, there were four other grade III events deemed not be caused by the experimental treatment. Using 18F-fluoromisonidazole (FMISO) positron emission tomography–computed tomography (PET–CT) before the start of buparlisib compared with similar assessment at day eight buparlisib monotherapy, the authors could demonstrate that PI3K inhibition reduced tumour hypoxia, which is suggestive for increased radiosensitivity. Radiotherapy was added to the experimental treatment after the second PET-CT. This proof of principle study nicely suggests that further research aiming to develop PI3K inhibitors as radiosensitisers should be encouraged. There is ample in vitro evidence for the rationale of this concept [2,3].

We would like to bring under the attention of your readership that buparlisib is not the ideal PI3K inhibitor to be used in this setting. In the recently reported Neoadjuvant Letrozole Plus Alpelisib or Buparlisib for Hormone Receptor Positive Human Epidermal Growth Factor Receptor 2 - Negative Breast Cancer (NEO-ORB) study (a prospective phase II randomised trial comparing neoadjuvant letrozole with or without alpelisib or buparlisib in hormone receptor–positive, human epidermal growth factor receptor–negative operable breast cancer), the buparlisib arm was stopped prematurely because of the nontolerable toxicity profile of buparlisib [4]. This decision was taken after a program-wide assessment of the safety and efficacy of this drug across different indications. In the NEO-ORB study, patients were treated with letrozole (2.5 mg once daily continuously) and either alpelisib (a selective PI3K alpha inhibitor, 300 mg once daily continuously), buparlisib (100 mg once daily continuously, later amended to 5 days on, two days of) or a placebo. Dose level reductions of buparlisib to 80 mg once daily or 60 mg once daily were allowed. Unacceptable liver toxicity and mood disorders were observed in the patients treated in the letrozole/buparlisib arm (N = 81). Grade III or more elevation of alanine aminotransferase and of aspartate aminotransferase was seen in, respectively, 39 (48.1%) and 28 (29.6%) cases versus one case (0.8%) in the placebo arm,

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whereas 12 patients had all grade depressive symptoms (versus 3 in the placebo arm). This is in line with observations in other studies [5,6]. Grade ≥III adverse events in the alpelisib arm (N = 130) were hyperglycemia (27%), rash (12%), maculo-papular rash (8%) and elevated transaminases (3.1%). Data on liver function tests are not given in the study by McGowan et al [1], and these authors note that only one patient had mood changes. The NEO-ORB study and several other studies clearly showed that selective PI3K(alpha) inhibition has more limited and better manageable adverse events compared with pan-PI3K pathway blocking [7]. We, therefore, would like to encourage future investigators in this very interesting field of radiosensitisation to avoid the use pan-PI3K inhibitors, in an attempt to make these treatments less toxic and more tolerable.

Conflict of interest statement

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