**Reviewer's report**

**Title:** Dronabinol has preferential antileukemic activity in acute lymphoblastic and myeloid leukemia with lymphoid differentiation patterns.

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**Reviewer:** Junya Kuroda

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**Major Compulsory Revisions**

The article “Dronabinol has preferential antileukemic activity in acute lymphoblastic and myeloid leukemia with lymphoid differentiation patterns” by bKampa-Schittenhelm et al. demonstrated that THC induced cell death in leukemic cells with CB1 expression in dose-dependent manner. The authors also suggested that THC preferentially exerted its antitumor activity on leukemic cells with lymphoid differentiation markers, however, the study was largely premature to definitely confirm their conclusion.

1. Despite the experiments with neutralizing antibody, more convincing experiments by means of genetic modification of CB1 (i.e. gene knockdown of CB1) should be added to validate CB1-mediated antileukemic effect of THC.

2. The role/functional significance of lymphoid markers in the effect of THC remained totally unclear. Was it accidental or functionally associated with CB1 expression?

3. In case CB1 (and/or CB2) was the therapeutic molecular target of THC in leukemic cells, it was unclear why THC induced cell death only in leukemic cells, but not brain cells, although both should express CB1 and CB2. Considering this point, I wonder if CB1 is the true molecular target in the antileukemic activity of THC. In case CB1 was the true target of THC in leukemic cells, authors need to explain/show why THC exerts different cellular effects between leukemic cells and brain cells.

4. Although authors insisted that THC induced apoptosis in leukemic cells, the assay for apoptosis was not appropriately assessed throughout the study, as the increase of Annexin-V-positive/PI-negative fraction (early apoptosis phase) was not indicated in Figure 2. With the data presented, it was unclear whether THC treatment increased cells undergoing late phase apoptosis or (early) necrosis without apoptotic process.

5. In addition, which pathway (mitochondria-mediated cell intrinsic pathway or death receptor-mediated cell extrinsic pathway) for apoptosis was activated by THC?

**Level of interest:** An article of limited interest
Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I have nothing to declare regarding the contents of this article.