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International Journal of Molecular and Immuno Oncology

New Drug Update

Amlodipine-induced inhibition of NFAT-2 nuclear translocation and its utility as an additive to immune checkpoint inhibitor

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Received: 01 May 2021
Accepted: 03 May 2021
EPub Ahead of Print: 06 Aug 2021
Published: 27 September 2021

DOI
10.25259/IJMIO_13_2021

Quick Response Code:

With the advent of immune checkpoint inhibitor and their success, especially in non-small cell lung carcinoma, a new stream started in the field of oncology, namely, immuno-oncology. This opened new vistas and understanding treatment of tumor immunology and ways to modulate it. Immune checkpoint inhibitor is still being assessed for the possible biomarker to predict response. Amlodipine, a dihydropyridine class calcium channel blocker (CCB), can be effectively repurposed as additive treatment to immune checkpoint inhibitors. We have assessed various case papers and case reports published who inadvertently prescribed CCB along with immune checkpoint inhibitor. We noticed that an excellent immune response was reported by these case studies. Although this evidence contributes little to our understanding of amlodipine as additive to immune checkpoint inhibitor, recent screening suggested amlodipine as candidate for being repurposed as immune checkpoint inhibitor.

This drug update is on addition of amlodipine to immune checkpoint inhibitor and its effects as well as side effects. We searched all the published literature on Google Scholar, PubMed, and other search engines using related search term.

CCBs like amlodipine have an action on calcineurin-calmodulin pathway.[1] This calcium-calcineurin-calmodulin pathway is one of the critical pathways in programmed death, that is, apoptosis.[2] Calcineurin-calmodulin-NFAT-2 pathways are important in T-cell-mediated cellular immunity. Any antigen presentation – say tumor antigen when presented to T cell, ameliorates cytoplasmic calcium-influx and calcineurin activation through calmodulin – a calcium-binding protein. This results in dephosphorylation of NFAT-2 a transcription factor. Dephosphorylated NFAT-2 enters nuclear domain and results in cellular response by inducing cytokine-like IL-2 secretion.[3]

T-lymphocytes are rich in calcineurin. Calcium channel plays a crucial role in inducing programmed death (PD) on cytotoxic T cells, thus managing to evade immune response to tumor cells. CCB through its effect on blocking calcium influx results in prevention of PD in cytotoxic T cells. Not only this but also CCB can reduce expression of PD-L1 expression on tumor cells.[4,5]

There is a case report of enhanced action of nivolumab with lenvatinib in intrahepatic cholangiocarcinoma with amlodipine as a comedication. Although this cannot be a conclusive evidence but powered by the knowledge of NFAT-2, calcineurin-calmodulin pathway, this

case report certainly raises eyebrows, regarding real-life efficacy of amlodipine in potentiating action of immune checkpoint inhibitor.[6] In this case, amlodipine 7.5 mg was prescribed inadvertently. There is no conclusive evidence of additive action of lenvatinib and nivolumab (immune checkpoint inhibitor), especially in cholangiocarcinoma. Amlodipine in this case was added after cycle 5, till cycle 20 of nivolumab lenvatinib. Although there was initial response, it was stable disease, it was maintained throughout cycle 20 of lenvatinib (8 mg) and nivolumab (3 mg/kg). In this case also, result became dramatic after cycle 5 when amlodipine was added. We again reiterate that it does not prove amlodipine and its action potentiating nivolumab-induced immune checkpoint inhibition. However, it certainly points to action of amlodipine and immune checkpoint inhibition.

In yet another case report, amlodipine with nivolumab in non-small cell carcinoma, here unfortunately, immune-mediated dermatologic effects were potentiated with nivolumab.[7] However, there are case series on dermatologic side effects of amlodipine and nivolumab. Early appearance of immune-related adverse effects (irAEs) is associated with better overall response rate and progression-free survival in non-small cell lung carcinoma.[8]

There are five types of voltage-gated calcium channels–L, N, P/Q, R, and T.[9] Dihydropyridines like amlodipine mainly act on L type of CCB.[9] In the past as well, these CCBs were studied for their role on apoptosis or PD. They were seen to be promoting apoptosis in colon adenocarcinoma cell line, lymphoma cell lines, and ganglioblastoma cell lines [Table 1],[10] but it reduced apoptosis in non-cancerous cells, it was confusing picture at that time. Later on, it was explained on the basis of immune evasion through NFAT-2 transcription and antigen presentation to cytotoxic T cells.[3]

CCBs have been known to have immunosuppressive and are incriminated to inhibit T-cell response.[11] In a study done on triple-negative breast cells (TNBCs) patients, it was observed that tumor infiltrated lymphocytes were significantly reduced in CCB-treated patients.[11] Although this study was done in pre-operative setting, which included all breast cancer patients including TNBC, there was no negative correlation of tumor infiltrating lymphocytes and CCBs in other breast cancer types, namely, her2 positive and luminal B type. The concerned study did not study overall survival of TNBC patients. Tumor immune microenvironment in TNBC is different than other solid malignancies.[12]

However, even in this case what is highlighted is PD-L1 action of amlodipine, its downregulation in particular. Amlodipine has immune modulating effect on T-cell lymphocytes through its mediation of NFAT-2 transcription factor. Hence, it has potential to be repurposed as additive to immune checkpoint inhibitors.

Various case studies, supportive evidence, and cancer cell lines have proved inhibitory role of amlodipine in glioblastoma,[13] melanoma,[14] and other cell lines. Only confusing picture is seen in TNBC where all other studies prove its beneficial role but one study done on TNBC, focusing on tumor infiltrating lymphocytes in patients given amlodipine for hypertension, showed reduced number of TILs in amlodipine-treated TNBC patients. This said study did not predict poor prognosis but suspected due to reduced TILs. TNBC tumor immune microenvironment is slightly different than other solid malignancies. TNBCs are largely heterogeneous disease and comprise various factors predicting response to immune checkpoint inhibitor.[15]

DOSE OF AMLODIPINE, PRODUCING IMMUNE CHECKPOINT INHIBITION

Single-agent amlodipine to act as immune checkpoint inhibitor, it needs to be given in high dose, in a study done on mice, it was given at the dose of 5 mg/kg, 10 mg/kg, and 15 mg/kg. Dose-dependent PD-L1 inhibition was seen.[16] However, its human equivalent is roughly around 5–10 mg/day, which is maximum tolerated dose of amlodipine,[17] the reason being different metabolism and long half-life.[17] Out of two enantiomer of amlodipine, S-enantiomer is more active as anti-PD-L1 as compared to R counterpart.[16]

As mentioned in Table 2, amlodipine was prescribed in all the above cases which reported good overall response, but with increased irAEs like TTP[18] and dermatologic side effects like acral vasculitis.[19]

However, an abstract published in ASCO reported higher incidences of acute kidney injury in patients treated with chemoimmunotherapy and dihydropyridine class of CCBs;[20] however, no details available as to how they reached this conclusion and were other factors contributing to AKI ruled out; and however, a caution must be taken while prescribing CCBs along with immunotherapy.

LOW-DOSE IMMUNE CHECKPOINT INHIBITORS AND ITS APPLICATION WITH AMLODIPINE

There are studies promoting low dose of immune checkpoint inhibitor without compromising the efficacy as PD-1 receptor is occupied even at low doses of ICI, and it transcends into flat drug-response curve.[21] In such situation, concomitant use although in hypertensive patients, we can see the additive effect of amlodipine to immune checkpoint inhibitor given in lower dosages.

Table 1: Organ-specific utility of amlodipine as additive to immune checkpoint inhibitor.

Organ	Role of amlodipine	Evidence
Non-small cell lung carcinoma	Numerous case studies suspected role of amlodipine as addition to immune checkpoint inhibitor, reduction of PD-L1 expression, NFAT-2 dephosphorylation[7]	Few case series and evidence are corroborative7
Colorectal carcinoma (CRC)	RKO and LoVo CRC cells showed decreased expression of PD-L1 Colorectal carcinoma shows high calcineurin expression[4]	Pre-clinical cell lines showed evidence of amlodipine
Glioblastoma	Amlodipine independently inhibited GBM cells, through the mediation of store operated calcium entry, caspase-3 – apoptotic protein[13]	Pre-clinical and *in vitro* studies show inhibitory role, no clinical study done
Triple-negative breast cancer	MDA-MB-231 showed decreased PD-L1 expression in cancer cell lines Decreased TILs seen in pre-operative cases of TNBC[11] No study proving its bad prognostic effect	Pre-clinical study shows its effect on cancer cell lines, one study on real-life patients showed statistically significantly low tumor infiltrating lymphocytes 11 in pre-operative cases of TNBC offered amlodipine with chemotherapy
Melanoma	PD-L1 expression on cancer cells decreased on A375 melanoma cancer cells Amlodipine inhibits uveal melanoma[14]	Pre-clinical study shows effect on melanoma

Table 2: Real world prescription of amlodipine with immune checkpoint inhibitors.

Case report	ICI cycles	Reported outcome
Intrahepatic cholangiocarcinoma[6]	20 cycles total amlodipine added after cycle 5	Good symptomatic benefit, decrease in liver lesion and stable bone mets after cycle 9
Melanoma	Nivolumab + ipilimumab	Amlodipine was prescribed due to uncontrolled hypertension – partial recovery noticed, no mention on overall response
Two cases of metastatic renal cell carcinoma	Nivolumab +ipilimumab	Good response but increase immune-mediated adverse effects
Metastatic renal cell carcinoma[18]	Nivolumab +ipilimumab	Excellent response with marked reduction in size of primary and metastasis- after 4th cycle developed Thrombotic thrombocytopenia purpura
Urothelial bladder carcinoma[19]	Tremelimumab + durvalumab for 4 cycles f/b durvalumab maintenance	Excellent clinical response for 10 months f/b acral vasculitis

CONCLUSION

We have sufficient data to investigate and retrospectively analyze immune checkpoint inhibitors and their effects with and without amlodipine. Various KEYNOTE, CHECKMATE, and IMpassion trials need to be analyzed with amlodipine, or other dihydropyridine agents given concomitantly and were the additive effect statistically significant? The question still remains! As for clinical point of view, if concomitant amlodipine is being prescribed, beware of immune toxicity, especially AKI but also a theoretical chance of better and durable outcome due to amlodipine is a possibility.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Zhang GQ, Zhu Z, Zhang W. Inhibitory effect of antihypertensive drugs on calcineurin in cardiomyocytes. Am J Hyperten 2009;22:132-6.
2. Harr MW, Distelhorst CW. Apoptosis and autophagy: Decoding calcium signals that mediate life or death. Cold Spring Harb Perspect Biol 2010;2:a005579.
3. Qin JJ, Nag S, Wang W, Zhou J, Zhang WD, Wang H, *et al.*

NFAT as cancer target: Mission possible? Biochim Biophys Acta 2014;1846:297-311.
4. Wu L, Lin W, Liao Q, Wang H, Lin C, Tang L, *et al*. Calcium channel blocker nifedipine suppresses colorectal cancer progression and immune escape by preventing NFAT2 nuclear translocation. Cell Rep 2020;33:108327.
5. Pan X, Li R, Guo H, Zhang W, Xu X, Chen X, *et al*. Dihydropyridine calcium channel blockers suppress the transcription of PD-L1 by inhibiting the activation of STAT1. Front Pharmacol 2021;11:539261.
6. Chen WX, Li GX, Hu ZN, Zhu P, Zhang BX, Ding ZY. Significant response to anti-PD-1 based immunotherapy plus lenvatinib for recurrent intrahepatic cholangiocarcinoma with bone metastasis: A case report and literature review. Medicine 2019;98:e17832.
7. Sidiropoulou P, Sgontzou T, Kostara I, Sgouros D, Theologi B, Zouridaki E, *et al*. A nivolumab in non-small cell lung cancer: A novel case of an erythema annulare centrifugum-like eruption. JAAD Case Rep 2019;5:572-5.
8. Bai R, Lv Z, Xu D, Cui J. Predictive biomarkers for cancer immunotherapy with immune checkpoint inhibitors. Biomark Res 2020;8:34.
9. Catterall WA. Voltage-gated calcium channels. Cold Spring Harb Perspect Biol 2011;3:a003947.
10. Mason RP. Calcium channel blockers, apoptosis and cancer: Is there a biologic relationship? J Am Coll Cardiol 1999;34:1857-66.
11. Takada K, Kashiwagi S, Asano Y, Goto W, Takahashi K, Fujita H, *et al*. Verification of the effects of calcium channel blockers on the immune microenvironment of breast cancer. BMC Cancer 2019;19:615.
12. Keren L, Bosse M, Marquez D, Angoshtari R, Jain S, Varma S, *et al*. A structured tumor-immune microenvironment in triple negative breast cancer revealed by multiplexed ion beam imaging. Cell 2018;174:1373-87.
13. Lee H, Kang S, Kim W. Drug repositioning for cancer therapy based on large-scale drug-induced transcriptional signatures. PLoS One 2016;11:e0150460.
14. Shaughnessy M, Lamuraglia G, Klebanov N, Ji Z, Rajadurai A, Kumar R, *et al*. Selective uveal melanoma inhibition with calcium channel blockade. Int J Oncol 2019;55:1090-6.
15. Thomas R, Al-Khadairi G, Decock J. Immune checkpoint inhibitors in triple negative breast cancer treatment: Promising future prospects. Front Oncol 2021;10:600573.
16. Li C, Yao H, Wang H, Fang JY, Xu J. Repurposing screen identifies amlodipine as an inducer of PD-L1 degradation and antitumor immunity. BioRxiv 2020;2020:117770.
17. Stopher DA, Beresford AP, Macrae PV, Humphrey MJ. The metabolism and pharmacokinetics of amlodipine in humans and animals. J Cardiovasc Pharmacol 1988;12:S55-9.
18. Ali Z, Zafar M, Wolfe Z, Akbar F, Lash B. Thrombotic thrombocytopenic purpura induced by immune checkpoint inhibitiors: A case report and review of the literature. Cureus 2020;12:e11246.
19. Comont T, Sibaud V, Mourey L, Cougoul P, Beyne-Rauzy O. Immune checkpoint inhibitor-related acral vasculitis. J Immunother Cancer 2018;6:120.
20. Baralo B, Hossain S, Ellangovan R, Kulkarni A, Keshava VE, Thirumaran R. The use of antihypertensive medications in cancer patients on chemo immunotherapy: Protection or not? J Clin Oncol 2020;38:e19238.
21. Renner A, Burotto M, Rojas C. Immune checkpoint inhibitor dosing: Can we go lower without compromising clinical efficacy? J Glob Oncol 2019;5:1-5.

How to cite this article: Gharote MA. Amlodipine-induced inhibition of NFAT-2 nuclear translocation and its utility as an additive to immune checkpoint inhibitor. Int J Mol Immuno Oncol 2021;6(3):145-8.