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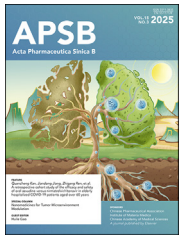

COMMENTARY

Evaluation of the efficacy and mechanisms of azvudine in elderly patients with malignant tumors complicated by COVID-19

KEY WORDS

Azvudine;
COVID-19;
Tumor;
Elderly

The COVID-19 pandemic, caused by SARS-CoV-2, has disproportionately affected elderly populations, especially those with comorbidities such as malignancies. Previous data indicated that individuals over 60 years account for >80% of COVID-19-related deaths, largely due to age-related immune senescence, chronic inflammation, and impaired antiviral responses[1-3]. Current antiviral therapies, including Paxlovid (nirmatrelvir/ritonavir), have limitations in this demographic: CYP3A4-mediated drug interactions, incomplete restoration of immune function, and insufficient efficacy in patients with cancer-related immunosuppression[2,4]. Azvudine, a nucleoside analog with dual antiviral and immunomodulatory properties[5], has emerged as a superior alternative in a large-scale cohort study of 5131 elderly patients, reducing all-cause mortality by 29% compared to Paxlovid (HR: 0.71) and demonstrating amplified benefits in malignancy subgroups (HR: 0.32)[2]. Here, we dissect azvudine's mechanisms underlying these survival advantages and their clinical relevance.

Aging is characterized by thymic atrophy and progressive depletion of naïve T cells, leading to diminished antiviral immunity and dysregulated inflammation[6]. COVID-19 exacerbates this deficit by depleting circulating $CD8^+$ T cells and amplifying exhausted T-cell populations, a phenomenon correlated with mortality[7]. Azvudine uniquely counters these defects through thymus-selective modulation. Preclinical studies reveal azvudine is phosphorylated in the thymus, enhancing the survival of $CD4^+$/$CD8^+$ T cells[5,7]. Clinically, azvudine-treated elderly patients exhibited higher peripheral lymphocyte counts, with a 68% mortality reduction in cancer patients[2]. By restoring T-cell numbers and functionality, azvudine mitigates the cytokine storm, preserves antiviral cytotoxicity, and rebalances immune homeostasis—critical in frail elderly individuals prone to immunopathology[2,7,8]. Using single-cell sequencing in a diethylnitrosamine (DEN) induced C57 liver cancer model (Fig. 1A), we demonstrated that azvudine increases the proportion of $CD8^+$ effector T cells and reduces the proportion of $CD8^+$ exhausted T cells, further indicating its potential to enhance T cell function in elderly patients (Fig. 1B−F).

Cancer patients face elevated COVID-19 mortality risks likely due to immunosuppressive tumor microenvironments (TMEs) dominated by regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and upregulated PD-L1 expression. Azvudine exhibits potential mechanism to counteract these barriers. It directly inhibits hepatocellular carcinoma (HCC) proliferation (*reduction in tumor volume and weight*, preclinical models)[8]. Moreover, scRNA-seq data from azvudine-treated HCC models demonstrate an increase in $MT2^+CD4^+$ T cells and a reduction in $CXCR6^+CD4^+$ T cells and $LY6C2^+CD8^+$ T cells[8], suggesting TME reprogramming. Similarly, we found azvudine significantly regulates CD8 T cells and CD4 T cells. Notably, it enhances the proportion and function of helper CD4 T cells, including the positive regulation of leukocyte activation, T cell differentiation, and ribosomal activation (Fig. 1G−I). In the clinical cohort, this action reduced composite disease progression by 46% in malignancy subgroups compared to Paxlovid ($P < 0.05$)[8].

Elderly patients often receive multiple medications, increasing risks of drug−drug interactions (DDIs)[9]. Paxlovid's reliance on

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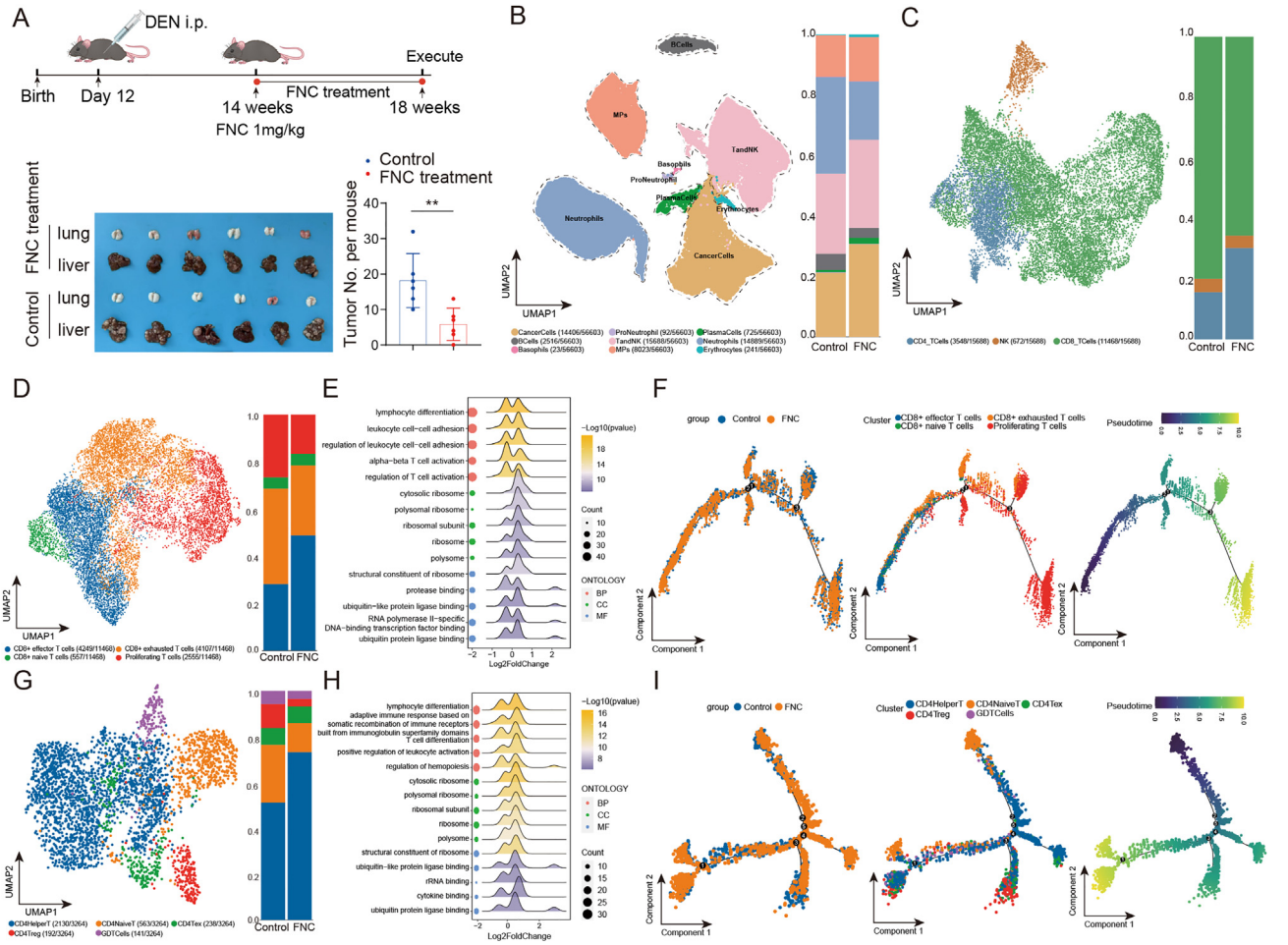

Figure 1 Azvudine affects tumor formation and alters T cell dynamics in DEN-induced HCC mouse model. (A) Schematic illustration of the establishment of DEN-induced HCC mouse model and azvudine treatment (top), representative images of resected lungs and livers (lower left), and the comparison of tumor counts between control and treatment groups (lower right, $^{**}P < 0.01$). (B) UMAP plot of annotated cell types and the proportion of these cell types in the control and azvudine-treated groups ($n = 3$ per group). (C) UMAP plot of T and natural killer (NK) cell subclusters and the proportion of annotated cell types in the control and azvudine-treated groups ($n = 3$ per group). (D) UMAP plot of $CD8^+$ T cell subclusters and the proportion of annotated cell types in the control and azvudine-treated groups ($n = 3$ per group). (E) GO enrichment analysis of the differentially expressed genes in $CD8^+$ effector T cells between the control and azvudine-treated groups ($n = 3$ per group). (F) Monocle 2 trajectory plot of $CD8^+$ T cell subclusters. Cells are colored by the groups (left), the cell clusters (middle), and the inferred pseudotime (right). (G) UMAP plot of $CD4^+$ T cell subclusters and the proportion of annotated cell types in the control and azvudine-treated groups ($n = 3$ per group). (H) GO enrichment analysis of the differentially expressed genes in $CD4^+$ helper T cells between the control and azvudine-treated groups ($n = 3$ per group). (I) Monocle 2 trajectory plot of $CD4^+$ T cell subclusters. Cells are colored by the groups (left), cell clusters (middle), and inferred pseudotime (right).

CYP3A4 metabolism limits its use with statins, anticoagulants, and so on[4]. Azvudine, conversely, is renally excreted, avoiding CYP450-mediated DDIs and enabling safer coadministration with oncology therapies. Clinical data confirm its superior safety: azvudine recipients experienced lower rates of hepatotoxicity (ALT elevation: 24% *vs*. 33%, $P < 0.001$; AST elevation: 19% *vs*. 25%, $P = 0.006$) and thrombocytopenia (11% *vs*. 16%, $P = 0.001$) than Paxlovid users[2]. Additionally, its prolonged half-life (up to 133 h) sustains antiviral activity beyond the critical 3−5-day treatment window, crucial for elderly patients with delayed viral clearance due to immunosenescence[10].

The retrospective cohort study provides compelling real-world evidence that azvudine outperforms Paxlovid in elderly COVID-19 patients, particularly those with malignancies[2]. Its thymic immunorestoration, antitumor activity, and pharmacokinetic safety collectively address the intersecting vulnerabilities of aging and cancer. Clinically, azvudine should be prioritized for elderly cancer patients, particularly those receiving CYP3A4-dependent therapies. Further research is warranted to: validate TME reprogramming mechanisms *via* longitudinal scRNA-seq in human cancer patients, optimize azvudine dosing in renal-impaired elderly cohorts, and explore synergies with immune checkpoint inhibitors to augment antitumor immunity post-COVID-19.

Azvudine represents a paradigm shift in managing COVID-19 among elderly cancer patients, merging antiviral efficacy with immunometabolic restoration. Its thymus-centric T-cell enhancement offers a multifaceted therapeutic strategy, while its low interaction profile ensures compatibility with geriatric polypharmacy. These findings advocate for azvudine's inclusion in first-line guidelines for high-risk elderly populations.

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Author contributions

Ranran Sun, Yihang Song, and Zhe Li contributed equally to this work. Ranran Sun wrote the manuscript, Yihang Song conducted the bioinformatic analysis, Zhe Li and Daming Wang performed experiments and interpreted the data, Zujiang Yu reviewed the manuscript and made significant revisions on the drafts. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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