Long term toxicity of therapy in Waldenström Macroglobulinemia

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The most frequently reported long-term toxicities of chemotherapy in WM are represented by the occurrence of second hematologic and non-hematologic cancers: therapy-related myelodysplasia/acute myeloid leukemia (t-MDS/AML), disease transformation into a diffuse large B cell lymphoma (DLBCL), and second solid tumors.

Cytotoxic agents associated with higher risk of these complications are the alkylating agents (AA) such as chlorambucil and cyclophoshamide, and the nucleoside analogues (NA) such as fludarabine and cladribine. The combination of fludarabine with cyclophosphamide or other alkylators may increase the risk of MDS/AML, due to their synergistic effect in producing DNA damage. The DNA damage of marrow progenitor cells may also account for the impairment of peripheral blood progenitor cell collection after prior fludarabine treatment. The median time to MDS/AML is 5 years. The prognosis of t-MDS/AML is generally poor, with a median survival of 5 months.[1]

Transformation of WM to DLBCL is another long term effect of cytotoxic agents. Several studies have underlined the role of fludarabine in increasing the risk of transformation to DLBCL. This oncogenic potential is enhanced by prior or concomitant alkylating therapy.

A higher incidence of second solid tumors seems peculiar to WM, as compared with other lymphoproliferative disorders, and is strongly correlated with the use of alkylating agents.[2,3] Disease related immunodeficiency and therapy related DNA damage have been postulated as mechanisms predisposing to second cancers.

Late adverse events related to rituximab (R) are uncommon in WM and are represented by late-onset neutropenia (LON), and by viral infectious complications such as hepatitis B reactivation, cytomegalovirus, herpes simplex virus, varicella zoster virus, and JC virus infection. LON is defined as grade III-IV neutropenia occurring at least 4 weeks after the last R dose. The incidence ranges from 3 to 27%.[4] LON episodes have been usually reported after NA-based immunochemotherapy, pointing to a role of NA-induced toxicity in myelosuppression.[5]

References

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