The Anticancer Drug Chlorambucil Interacts with the Human Erythrocyte Membrane and Model Phospholipid Bilayers

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The plasma membrane has gained increasing attention as a possible target of antitumor drugs. It has been reported that they act as growth factor antagonists, growth factor receptor blockers, interfere with mitogenic signal transduction or exert direct cytotoxic effects. Chlorambucil (4-[*p*-(bis[2-chloroethyl]amino)phenyl]butyric acid) is an alkylating agent widely used in the treatment of chronic lymphocytic leukaemia. Contradictory reports have been published concerning its interaction with cell membranes. Whereas a decrease in the fluidity of Ehrlich ascite tumor cells has been adduced, no evidences were found that chlorambucil changes membrane lipid fluidity and alkylating agents had effects in these systems even at highly toxic concentrations. Our results showed that chlorambucil at a dose equivalent to its therapeutical concentration in the plasma (3.6 μM) caused the human erythrocyte membrane to develop cup-shaped forms (stomatocytes). Accordingly to the bilayer couple hypothesis, this means that the drug is inserted into the inner monolayer of the erythrocyte membrane, a conclusion supported by X-ray diffraction performed on multilayers of dimyristoylphosphatidylcholine (DMPC) and dimyristoylphosphatidylethanolamine (DMPE), representative of phospholipid classes located in the outer and inner monolayers of the erythrocyte membrane, respectively. It is concluded that the cytotoxic effect of chlorambucil might be due to alteration of the structure and therefore of the physiological properties of cell membranes such as fluidity, permeability, receptor and channel functions.