CURRENT CLINICAL PROGRESS WITH NEW AGENTS: ALKYLATING AGENTS

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INTRODUCTION

The first report on the biological effect of alkylating agents was published as early as in 1887 /1/. Almost fifty years elapsed until it became known that sulphur mustard had antitumor effect against experimental solid tumors /2/, and the first clinical observations on the potential usefulness of alkylating agents were recorded in 1946 /3/. Since the first successful application of nitrogen mustard in haemopoietic malignancies thousands of molecules with alkylating capacity were synthetized and most of them have shown remarkable antitumour properties. Nevertheless, it became very soon obvious that their selectivity is poor and their therapeutic activity, therefore, was limited. Consequently the view is now being expressed that the future progress would seem to lie in the discovery of compounds that are toxic towards a limited range of neoplasms /4/. Such substances do exist among the methanesulfonates /busulphan/, hexitol derivatives /dibromomannitol/ or nitrosoureas /streptozotocin/ and were recently synthetized in other classes of alkylating agents as well /quinométhylacridines/. This review deals with those alkylating agents which are currently undergoing clinical trials. From the survey nitrosoureas are omitted being previously discussed. However, some of the recently produced compounds with unidentified mechanism of action are incorporated into the review.

**Cyclophosphamide analogues**

Cyclophosphamide /CPM/, one of the most well tolerated cytostatic agents acted as parent compound for the synthesis
of further analogues such as ifosfamide, trofosfamide, sulfosfamide, ASTA B 516 and ASTA B 707. Among them only ifosfamide /Holoxan/ deserved special attention. This drug \([\text{I}]/3-/2\text{-chloroethyl}/2-/2\text{-chloroethylamino}/-\text{tetrahydro-}\text{H}-1,2,3\text{-oxaphosphorine-2 oxide}/\) was found to be inactive \textit{in vitro} and for antitumour activity requires metabolism by liver microsomal enzymes. The metabolic procedure is, however, prolonged and so is its action in comparison to CPM. Animal data showed favourable antitumour properties identical to that of the parent compound. The uroepithelial toxicity of ifosfamide could be dramatically reduced by sodium-2-mercaptopetoethanesulphate /MESNA/ /5/. Thus, its clinical use was promising. According to broad phase II studies it is active in breast, ovarian and small cell lung cancer. Recent phase III studies demonstrated its effectiveness in combination with VP-16213 in therapy resistant lung, ovarian and testicular cancer as well /6/.

\textbf{Nitrogen mustard analogues}

Among these analogues 'steroid-N-nitroso-omega-haloalkyl-carbamates have to be discussed due to their clinical significance. In a series of chemicals containing a glucocorticoid esterified with nitrogen mustards \textit{prednimustine} became of wide clinical interest. The rationale in designing this compound was to combine two individually active antitumour agents, in this case prednisone and chlorambucil /7/. A broad phase II trial organized by the EORTC revealed antitumour activity in malignant lymphomas, and marginal tumor responses were also seen in melanoma and bronchial cancer. In another trial 35 \% response rate was observed in hormone resistant advanced prostatic cancer /8/.

\textbf{Dialkyltriazenes}

Among dialkyltriazenes DTIC /5-/3,3-dimethyl-triazino/-imidazol-4-carboxamide is still the only widely used antitumour agent. Its di-2-chloroethyl analogue: BTIC has been subjected to phase I trials without convincing results. The clinical application of dialkyltriazenes seems to be