South African Medical Journal : Suid-Afrikaanse Tydskrif vir Geneeskunde

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CHEMOTHERAPY OF CANCER — I. ANTITUMOUR DRUGS

While the term chemotherapy, as applied to tumours, can include treatment by hormones, it is perhaps best reserved for the more obviously cyto-destructive agents. As such the method is now nearly a hundred years old and dates from Lissauer's discovery of the effect of potassium arsenite on leukaemia.[1]

The best known and most widely used compounds are the alkylating agents, so called because they contain alkyl groups (e.g. CH_2CH_2Cl in mustine) in a highly active form, which produce their effects by combination with essential cell constituents. There are three great groups of these compounds, the sulphonic acid esters (e.g. 'myleran') the ethyleneimines (notably TEM and 'thiotepa'), and the third and largest group, the chloroethylamines or mustards. The latter may be of several different types, the best known being simple aliphatic mustine, nitrogen mustard or HN_2 (originally a wartime code name),[2] aromatic forms such as chlorambucil, the sugar mustards such as mannomustine (or 'degranol'), or those with an inactive carrier group, which is thought to be digested off at the site of action (e.g. 'endoxan'). Many others have been prepared, such as quinacrine and chloroquin mustard and the sulphur mustards, but have not generally found acceptance in clinical practice. A newcomer of promise is *l*-phenylalanine mustine ('melphalan'). These varying series of compounds were synthesized in attempts to produce greater localization within the cell, and hence more specific action, by easier transport across the cell membrane or activation or release within it, e.g. endoxan. Galton has pointed out that this presupposes an increased concentration of enzymes within the neoplastic cell[3] — a point yet to be proved. However, a number of them by their peculiar properties have shown themselves suitable for special applications, e.g. chlorambucil as an oral preparation and melphalan as a safe intravascular agent. The use of uracil mustard, where the mustard group is attached to the pyrimidine base, is a new approach to the problem of specificity and has recently been shown to be effective in the treatment of the malignant reticuloses.[4] It may be that the side-effects are less.

Larionov[5] has suggested that the racemic form of phenylalanine mustine (or sarcolysin) may act in two ways — as a mustard and as an amino acid. This would introduce a new class of compounds, the alkylating metabolites. Not all would agree with him.[6] This agent has been found to be effective in the treatment of seminoma and Ewing's tumour.[7]

According to the number of available alkyl groups per molecule, the alkylating agents can be classed as mono- or multifunctional. The latter are far more active *in vivo*, possibly owing to cross linking of the DNA of the resting chromosome by the several active arms.[8] Ross[9] has pointed out that the linkage may take place between the phosphate groups rather than the sulphydryl and amino groups. Evidence has also been put forward of interference with DNA formation, possibly by inhibiting the phosphorylation of mononucleotides or their polymerization to polynucleotides, but RNA is not exempt.[10] Not all these agents act in the same manner, and Galton and his colleagues[11] have brought evidence to show that myleran acts continuously throughout the cell cycle while chlorambucil acts at the end of the resting phase. This may be due to interference with nucleic-acid synthesis at different stages — the mustards causing disorganization of already formed nucleic acids, and myleran preventing their synthesis.[12] The effect may be upon enzymes and not upon their substrates.[13] Various authors have reported upon the rapid and transient effects of the mustines.[14,15] With mannomustine, depression of mitosis is found in six to twenty-four hours and a maximum effect in forty-eight to seventy-two hours. There is nuclear and cellular disintegration, followed by anomalous mitoses and giant-cell formation. DNA activity probably returns to normal levels within ninety-six hours.

It has been assumed that the appearance of abnormal cell forms following treatment with alkylating agents could be equated with severe biological damage or even biological cell death, but recent work suggests that this may not be so.[15,16] Similar changes may be found after radiation, and for this reason (as well as others, such as bone-marrow depression, epilation, erythema induction, membrane formation, and mutation induction) these compounds are called radiomimetic. It has been estimated that the whole-body (especially the bone-marrow) effects of a course of mustine are similar to a whole-body dose of about 150r. The dosage for regional infusion of mustine can be roughly estimated according to the volume/time/dose relationships of radiotherapy, and the clinical responses are very much the same. From this information it could be inferred that perfusions lasting a few hours to a few days would be unlikely to produce permanent effects on the tumour, and this has been found to be the case.[8] This problem cannot be overcome by increasing the amount of the drug perfused, since the tolerance of the normal tissues can be exceeded with damage to blood vessels, skin, and nerves. The neurotoxic effect of mustine is well known, both for the central and peripheral nervous systems. The effects of cytotoxic drugs are quicker than those of radiotherapy given in conventional dosage, but this may be a question of relative effective dosage.

The antimetabolites provide the other great class of antitumour drugs. They exert their effects by closely simulating various essential substances and hence block their uptake by the cell. Probably the best known is amethopterin (methotrexate), a folic-acid antagonist, which contains the 4-amino group[17] and inhibits the conversion of folic acid to folinic acid, an essential agent in purine

and pyrimidine synthesis. Displacement of folinic acid has been demonstrated.[18] In all antitumour drugs, resistance is a problem, and acquired resistance in this case may arise from dependance upon the drug.[19]

Renewed interest in this agent followed reports of Li, Hertz and Spencer[20] of its use in choriocarcinoma, and this work has recently been reviewed.[21] It would appear that the great majority of patients treated will undergo remission, and in about half this will be complete. This makes methotrexate the drug of choice in the treatment of the disseminated form of the disease, provided the tumour masses are not large. If they are, X-ray therapy, either as a preliminary or alone, is to be preferred. Intra-arterial regional infusion for squamous carcinoma has also been reported[22,23] and, while early reports do not appear to be encouraging, it is likely to be valuable in combination with other forms of treatment, either cytotoxics or X-ray therapy.

The most commonly used purine analogue is 6-mercaptopurine, especially in the treatment of acute leukaemia. Several recent reports recount its use, in combination with methotrexate, in the treatment of choriocarcinoma.[24-26] There is however no clear evidence that the two agents are more effective than methotrexate alone, and the risks of bone-marrow damage are presumably higher. This combination appears to be of enhanced value in the treatment of childhood leukaemia, but not in acute leukaemia in adults, where 6-mercaptopurine remains the agent of choice.[27] 5-fluro-uracil is an example of the fluorinated pyrimidines[28] and, by blocking the 5 methylation of uracil to thymine, represents yet another class of antimetabolites. It is highly toxic, but may be of use against large-bowel tumours[29] and in combination with X-ray therapy.[30,31] An aminopyrimidine ('daraprim') has been reported to be of some use in the treatment of polycythaemia vera,[32,33] but does not appear to be as reliable as P^{32}. Nevertheless, in the rather unlikely event of P^{32} being shown to alter the leukaemia rate in polycythaemia vera[34] significantly, it may be a possible alternative method of treatment, especially in younger patients.

Lastly, there is a heterogeneous collection of drugs of which two deserve mention — actinomycin D and vincaleukoblastine. The former is one of a series of antibiotics isolated from an actinomyces,[35] and possibly its mode of action is by interference with coenzyme A,[36] RNA synthesis, and the nucleolus.[37] It has been reported to cause regression in Wilms's tumour, rhabdomyosarcoma, and neuroblastoma.[38,39] When given concurrently, it increases the sensitivity of the patient's tissues, and perhaps that of the tumour, to X-ray therapy. Vincaleukoblastine is an alkaloid isolated from the shrub known as the periwinkle. It may interfere with glutamic-acid metabolism in the citric-acid and ornithine cycles and be of use in otherwise resistant Hodgkin's disease.[40,41]

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MEDIESE EN PSIGIATRIESE IMPLIKASIES VAN LYFSTRAF

Die probleem van die beheer van menslike gedrag deur die toepassing van lyfstraf in die een of ander vorm, word van tyd tot tyd teen die agtergrond van sterk emosionele gevoelens bespreek — in ons eie land en in baie ander lande van die wêreld. As geneeshere wat daagliks te doen kry met die gedragsprobleme van volwassenes sowel as van kinders, kan ons ons nie heeltemal losmaak van die implikasies van hierdie probleem nie.

Die uiterste vorm van lyfstraf — die doodstraf — is 'n onderwerp waarop gereken kan word dat dit hewige emosies na vore roep by die bespreking daarvan. En alhoewel dit eintlik die gebied van die strafregtelike deskundige is, voel 'n groot aantal persone genoodsaak om 'n stuiwer in hierdie beurs te gooi. Die onlangse besluit om die doodstraf in Nieu-Seeland af te skaf, het byvoorbeeld heftige bespreking dwarsoor die wêreld tot gevolg gehad.

Wat ons in hierdie verband sou wou doen, is om aan te toon dat die probleem van doodstraf besondere interessante implikasies het wat betref die motivering en beheer van menslike gedrag. Dit is 'n onderwerp wat bestudeer moet word in al sy fasette en teen die omlysting van beskaafde norme van menslike etiek, aan die een kant, en die wisselende maatstawwe van verskillende beskawingstandaarde, aan die ander kant. Ons sou wou voorstel dat hier 'n vrugbare veld van navorsing is, nie net vir die strafregtelike amptenaar nie, maar ook vir die psigiatriese en maatskaplike navorser wat belang stel in die moontlikheid van die verenigbaarheid van algemeen-menslike standaarde met groeps- en gebiedsnorme.

Die probleem van lyfstraf vir jeugdige oortreders het ook al in ons land, soos elders, groot opspraak verwek. Aan die een kant is daar diegene wat in lyfstraf 'n goeie

metode sien waardeur die hof die toenemende wetteloosheid en veral die neiging tot geweld in bedwang kan hou. Aan die ander kant is daar diegene wat teen swaar lyfstraf, veral vir jeugdiges, gekant is. In Engeland is onlangs 'n amptelike ondersoek ingestel deur die betrokke staatsdepartement.[1] Na sorgvuldige oorweging van al die gegewens, dui hierdie ondersoek daarop dat dit twyfelagtig is of lyfstraf 'n nuttige doel dien in terme van korrektiewe behandeling. Hierdie bevinding dien ook weer om ons aandag te vestig op die groot behoefte wat ons veral in hierdie land het (waar daar so baie groepe van persone in maatskaplike en kulturele oorgangstadiums is), aan leiding en voorligting deur geskoolde maatskaplike werkers en sielkundiges. Ons leef in 'n steeds veranderende wêreld wat betref die daaglikse geestelike en ekonomiese milieu van groot groepe persone, en die verpligting rus op ons om die onderhawige probleme steeds te bly interpreteer in terme van die lig, nie net wat ons het nie, maar ook wat ons behoort te hê.

'n Ander belangrike faset van die probleem van lyfstraf is die kwessie van lyfstraf op skool. In hierdie verband is daar ook onlangs in Engeland 'n interessante studie[2] gemaak. Dertig skole is gekies waarvan die helfte as ‚goeie' skole beskou is in terme van die gedrag van die kinders, en die helfte as ‚swak' skole. Navraag is toe gedoen[3] om uit te vind hoe die ‚lat' in die skole gebruik word — nl. of ligte, medium, of swaar lyfstraf gebruiklik was. Ook is die kinders uit elkeen van die skole wat in die jeughof beland het, bestudeer. Die hoofbevinding van die ondersoek was dat die gedrag van die kinders nie noodwendig saamhang met hul maatskaplike agtergrond nie, en dat die gedrag van die kinders die beste is en oortreding die minste voorkom in daardie skole waar lyfstraf spaarsaam gebruik word.

Hierdie bevinding dui natuurlik direk op die betekenis van die kwaliteit van die onderwysers. Nie die lat nie, maar 'n goeie onderwyser, is die primêre beherende en inspirerende faktor.

In Suid-Afrika (en as mediese professie kan ons nie afsydig staan daarteenoor nie), is ons besig om 'n grootskaalse erosie te sien van ons beste mannekrag — die onderwysers. Ons lees gereeld skokkende berigte oor die groot tekort aan onderwysers. Deur hierdie tekort kan ons nie anders nie as om aan die verloorkant te bly — wat die algemene kulturele opvoeding van ons kinders betref, sowel as hul voorbereiding as emosionele-volwasse persone.

Die tekort aan onderwysers bly akuut deurdat so 'n groot aantal belowende jongmense òf hulle nie aanmeld as rekrute nie, òf die onderwys verlaat vir meer lonende werksomstandighede. As 'n nasie kan ons hierdie toestand van sake nie laat voortduur nie. Ons moet die onderwyser, wat sy amp en status betref, erken as ons waardevolste besitting. Ons moet hom help om sy ereplek as opvoeder en kultuurleier te behou en te handhaaf, en ons moet hom dienooreenkomstig beloon — ook finansieel. Ons kan nie toelaat dat die onderwyser — soos wat dit tans die geval is — swakker beloon word as werkers in die meeste ander beroepe en bedrywe nie. Ons het ten opsigte van die onderwysers van ons volk 'n groot beskawingskuld wat ons moet delg. En ons moet dit gou doen of ondergaan as beskaafde nasie.

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