EDITORIAL / VAN DIE REDAKSIE

A cancer control programme for South Africa

In September 1993 the Cancer Association of South Africa (CANSA), under the able leadership of Professor Frans Geldenhuys, convened a landmark 3-day Cancer Control Workshop in Midrand with international participation, to consider the establishment of a national cancer control programme for South Africa according to the policies and guidelines laid down by the World Health Organisation. With representatives from the medical schools, the Medical Research Council, the South African Institute for Medical Research, the late Department of National Health and Population Development, the provincial administrations, the hospice movement, a variety of non-government organisations and several other instances, the workshop was arguably the largest indaba ever convened on the subject of cancer prevention in South Africa. Of special significance was the attendance at the workshop by Professor Jan Stjernswärd, the Swedish-born WHO representative and cancer expert; Ms Jeanette Webber of the McMillan Cancer Relief Trust in the UK; and Dr Gustav Wolvaardt of the South African Permanent Mission to the WHO. Dr Derek Yach served as the proceedings recorder.

The workshop first reviewed the existing cancer situation in South Africa: the epidemiology of cancers prevalent in this country; lifestyle and environmental risk factors; organisations and other resources available for the campaign against cancer; possible means of cancer prevention, education and early detection and so on. The workshop then identified cervical, skin, breast and lung cancers as the most targetable malignancies in South Africa in terms *inter alia* of the magnitude of the problem; preventability and/or early detectability; and ready access to and efficacy of early therapeutic intervention. Cervical carcinoma provides a good example of targetability: more women die of cervical cancer than men and women combined who die of AIDS in the world each year, yet cervical cancer is preventable, can be detected early and can be treated successfully. Six other cancers (oesophagus, liver, prostate, large bowel, lymphoma and mesothelioma), whose early detection and preventability remain unclear or controversial, were recommended for further research to determine whether they should receive priority in a national cancer prevention scheme.

The workshop then looked into the feasibility of a national cancer control programme (NCCP) for South Africa: why we need it, what its goals and objectives should be, who should be involved and how its impact should be monitored. There was acknowledgement that there is at present no coherent national policy on primary cancer prevention, and no linkage of all the organisations concerned with cancer prevention or management into a national network. No national priorities have been set, and no consensus has been reached on those conditions that may or may not be preventable or detectable at an early stage.

The purpose of the NCCP would be to initiate, coordinate and monitor cancer control activity across the country, to liaise with government and other interested parties, and to consolidate fund-raising campaigns. The NCCP would work towards the reduction of lifestyle risk factors (tobacco smoking, alcohol abuse, bad dietary practices, excessive sunlight exposure, risky sexual behaviour, etc.) and environmental factors (occupational exposure, air pollution, radiation, water pollution and food contaminants) known or suspected to cause cancer. Thus, the NCCP would support a ban on advertising cigarettes, sponsor education of the youth on smoking, and lobby against the subsidisation of tobacco farmers. The NCCP would pursue health promotion in a holistic manner, and in accordance with the Ottawa Charter.

The NCCP would be drawn from CANSA and from those organisations with an interest in the prevention, detection, research and treatment of cancer. It would maintain an office initially at CANSA, and would be headed by a 'Cancer Tzar' funded by the Department of Health, but independent from it. The NCCP would be subject to ongoing monitoring and periodic review, and its effectiveness measured in the light of National Cancer Registry data, and in terms of the outcomes of specific projects. The NCCP would be the clearing house for all cancer programmes in South Africa, and would be responsible for co-operation with international organisations such as the WHO.

It was generally recognised that to put together a coherent national cancer policy and establish an NCCP there would be a need to cultivate political will and commitment. To this end, the proposals regarding the NCCP were to be presented to the National Health Forum as well as to the health minister of the new government. There was a strong commitment of support and assistance from the WHO representative. The *SAMJ* congratulates and supports CANSA in this initiative, and hopes that the plans mooted in Midrand are beginning to take shape.

D. J. NCAYIYANA

Recent advances in the management of acute leukaemia in adults

Striking progress and advances in the management of acute leukaemia have occurred in the last 2 - 3 decades.[1,2] Prior to this period, acute leukaemia was generally regarded as an incurable disease. Today, appropriate therapy allows 65 - 90% of patients with acute lymphoblastic leukaemia (ALL) and 50 - 80% of patients with acute myeloid leukaemia (AML) to achieve complete remission. Prolonged disease-free survival without recurrence of disease (tantamount to cure) is possible in approximately one-third of adults with ALL and 10% of patients with AML. This is particularly true of younger adults with favourable prognostic factors. Although higher cure rates are the goal for the future, the present situation represents a significant advance compared with the dismal prognosis associated with acute leukaemia a few decades ago.

Such substantial progress has resulted from improvements in the understanding of the biology of the disease, the development of newer diagnostic techniques which allow more accurate definition of prognostic factors, improved supportive care, the discovery and development of more effective chemotherapeutic agents (including differentiating agents and biological response modifiers) and, more importantly, the rational use of these and existing therapies, as well as the wider applications of bone marrow transplantation as an effective post-remission strategy. All these factors have contri-

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buted to the improved cure rates observed in acute leukaemia.

Management of patients with acute leukaemia should be initiated promptly, at a specialised centre, by an integrated, multidisciplinary health care team. The two principal arms of treatment are supportive measures and specific therapy. Supportive measures are primarily aimed at prevention and management of the haemorrhagic and infective complications of the severe myelosuppression associated with therapy or disease. Improvements in blood component therapy (especially the availability of platelet concentrates), use of broad-spectrum antimicrobial agents, specialised nursing care, antiseptic measures and the recent introduction of haematopoietic growth factors have all contributed to the decline in morbidity and mortality that accompany bleeding and infection. Use of haematopoietic growth factors such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) is associated with accelerated neutrophil recovery, shorter period of neutropenia and reduction in the frequency of infection and the need for intravenous antibiotics.[3] These agents also allow for more intensive therapy to be administered in a safe manner.[4,5] Other aspects of the overall management of the patient (e.g. psychosocial, nutritional) should not be overlooked.

Specific therapy is conveniently divided into two phases: remission induction therapy and postremission therapy. The gold standard in remission induction therapy in AML involves a combination of cytosine arabinoside and daunorubicin, with or without thioguanine. A complete remission rate of 60 - 75% is possible with this regimen.[6] Various approaches have been employed in order to improve the remission rate or extend the remission duration. These entail increasing the dose or duration of cytotoxic therapy (e.g. cytosine arabinoside), substitution of existing drugs by newer or equivalent agents (e.g. daunorubicin by idarubicin or mitoxantrone) or the addition of other agents (e.g. etoposide) to the standard regimen.[7-10] More recently high-dose, short-course chemotherapy has been used (e.g. high-dose cytosine arabinoside and high-dose mitoxantrone, with or without etoposide) in an attempt to improve the 'quality' of remission.[11] Whether such intensive therapy is associated with acceptable toxicity and whether a better 'quality' remission will translate into higher overall cure rates is currently unknown, and is the subject of ongoing trials.

The primary goal of therapy in ALL is cure. Although this can be realised in 60 - 70% of children, the outlook in adults is less favourable. Approximately one-third of adutls achieve long-term cure. Complete remission rates of 65 - 90% are possible with ALL remission induction therapy, using prednisone, vincristine and an anthracycline.[12] The addition of L-asparaginase to the above three-drug combination does not affect the remission rate, but improves remission quality. The outcome in certain ALL subgroups has improved with the inclusion of cyclophosphamide and cytosine arabinoside for T-ALL, and high-dose methotrexate for B-ALL.[13-15] More intensive therapies employing high-dose cytosine arabinoside, high-dose methotrexate, etoposide and anthracyclines have resulted in prolongation of remission and increases in disease-free survival rates, as well as a decrease in the proportion of patients with resistant disease.[16]

Once remission is attained, further therapy is necessary to eradicate subclinical residual disease and prevent relapse. Postremission therapy has resulted in prolongation of remission duration compared with no therapy at all. More effective therapy during this phase is likely to have a major impact on long-term survival. Current therapeutic approaches include chemotherapy and bone marrow transplantation.

In AML, more intensive chemotherapy (high-dose, short-duration chemotherapy referred to as intensification and administered for 1 - 3 cycles) is a current trend that is now being favoured in preference to consolidation and maintenance therapy. Recent studies have demonstrated no survival advantage with maintenance treatment, and prolongation of remission duration is probably a measure of early postremission therapy rather than continued maintenance.[17,18] It is useful to stratify patients into low- and high-risk categories based on the presence of adverse prognostic factors, so that a risk-directed approach may be employed where possible. In low-risk patients (*de novo* AML, young age group) the probability of disease-free survival 3 or more years after bone marrow transplantation does not differ significantly from the results obtained with intensive postremission chemotherapy. In such patients, allogeneic bone marrow transplantation should be delayed until documentation of early first relapse. In high-risk patients (secondary AML, adverse cytogenetic abnormalities, etc.) under the age of 55 years, who have a high probability of relapse, bone marrow transplantation should be considered in first remission. It should also be considered in relapsed and refractory AML. Allogeneic bone marrow transplantation is still regarded as the most definitive (curative) therapy in AML because of the low rate of relapse. However, it is only feasible in 10 - 20% of patients. As a consequence of this, the scope has broadened to include autologous bone marrow transplantation and, as an alternative to marrow stem cells, the use of peripheral blood stem cell rescue following marrow ablation from high-dose chemotherapy.[19-21] The precise role of these latter approaches is likely to become clear in the near future.

Age is a major adverse prognostic factor in AML, with elderly patients generally achieving a lower remission rate and shorter survival. In most series, elderly patients (>60 years) account for more than a third of the total number, and therefore constitute a large group of patients. Therapeutic options in the elderly are still unclear and pose a major challenge. Some of the therapies advocated include use of conventional chemotherapeutic regimens, shortening the duration and attenuating the dose of therapy, substitution of daunorubicin by other anthracyclines (e.g. idarubicin or mitoxantrone), and the use of low-dose chemotherapy and palliation.[22,23]

In ALL likewise, more intensive therapy is favoured in the postremission phase, especially in high-risk groups, as this may nullify some of the poor prognostic factors and enhance long-term survival.[16,24] Unlike AML, central nervous system prophylaxis and maintenance are established forms of therapy in ALL. The benefit of maintenance therapy appears to be greater in low-risk patients than in high-risk groups (e.g. Philadelphia (Ph') positive and B-ALL). In such individuals, short intensive protocols may be more appropriate, with early recourse to bone marrow transplantation (i.e. in first remission).[25,26] An alternative approach in Ph'-positive ALL entails the use of α-interferon in an attempt to maintain remission.[27] Bone marrow transplantation should also be considered in relapsed and refractory ALL.

No current review of acute leukaemia is complete without mention of acute promyelocytic leukaemia (APL), a subtype of AML with distinctive clinical, morphological and biological features. The disease is characterised by a bleeding diathesis (disseminated intravascular coagulopathy), a balanced translocation involving chromosomes 15 and 17 and leading to fusion between two nuclear transcription factors, viz. PML (promyelocytic leukaemia) from chromosome 15 and RARα

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(retinoic acid receptor alpha) on chromosome 17. This results in two fusion genes, PML\RARα and RARα\PML. The former fusion protein is thought to be responsible for the differentiation block of the leukaemic blasts at the promyelocyte stage and the striking efficacy of retinoic acid to the differentiating activity.[28-30] Complete remission rates of 50 - 80% are possible in APL with conventional chemotherapy and improved supportive care. Mortality resulting primarily from haemorrhage is a major problem in the remission induction period.

Use of retinoic acid in the induction phase results in rapid improvement in the coagulation defect, a decrease in mortality and a higher remission rate. Once remission is achieved, survival is often longer compared with other AML subtypes.[31] Long-term therapy with retinoic acid is associated with relapse and resistance to subsequent treatment as well as a number of potential side-effects. Currently, retinoic acid is recommended for remission induction only. Combination chemotherapy should be administered in the postremission phase.[29-32] The role of cytokines and alternative retinoids is currently being investigated.

Research in APL has provided new insights into leukaemogenesis. Having defined the molecular lesion it is now possible to target appropriate therapy at the defect, and to utilise the molecular defect as an indicator of residual disease. The discovery of sensitive methods to detect minimal residual disease (e.g. *in situ* hybridisation, polymerase chain reaction) represents a major advance, as this allows assessment of the effectiveness of therapy and assists in planning future therapy. Further progress in acute leukaemia will depend on the effectiveness of early intensive therapy in improving the cure rate, greater application of the haematopoietic growth factors and biological response modifiers such as α-interferon and the interleukins, e.g. IL-2, IL-4 and IL-7, and devising better methods of circumventing or overcoming multidrug resistance, which is an important cause of treatment failure.

In the local context, what is required is a flexible and rational approach in the management of acute leukaemia. Careful consideration of individual risk factors in the context of the available resources is necessary, in order to tailor appropriate therapy.

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