MOPP AND OTHER COMBINED CHEMOTHERAPY INCLUDING ALKYLATING AGENTS (Group 1)

A. Evidence for carcinogenicity to humans (*sufficient*)

In 1972, roughly five years after the introduction of intensive combined chemotherapy for Hodgkin's disease, the first report of subsequent acute nonlymphocytic leukaemia (ANLL) appeared[1]. Since then, investigators in more than 15 clinical centres and collaborative treatment groups in Europe and North America have performed a series of studies leading to the conclusion that the association is probably causal.

These studies are not easily compared with one another. The groups and subgroups of study subjects differ in distribution by age, stage at diagnosis, timing of initial therapy (both radiological and chemotherapeutic), interval between diagnosis and intensive chemotherapy, composition of the chemotherapeutic regimen and length of follow-up. Further, the methods of counting and allocating patients or person-years at risk, the criteria for diagnosis, the method of validating the separate identity of a second malignancy, the

'unexposed' group used as a reference standard, the method of statistical analysis, and the index used to summarize risk differences vary greatly from study to study. Finally, the extent to which such specific details are clearly described in the published reports is also variable.

Nonetheless, these reports are consistent in describing a strongly increased risk of ANLL after intensive treatment with combined chemotherapeutic regimens, particularly those containing alkylating agents. The most recent reports[2-18] describe a total of over 11 000 patients, reported roughly a decade after diagnosis, among whom more than 170 cases of ANLL have thus far occurred. About one-quarter of these patients had received no intensive combined chemotherapy, yet all but a few leukaemia cases have occurred among those patients who did. Summary estimates of the relative risk of ANLL after intensive chemotherapy (relative to reasonably appropriate healthy populations) have been calculated to vary from 9[11] through 40[4,10] to well over 100[6,9,16], precluding meaningful comparisons between studies, and estimates of the absolute (actuarial) risk observed in the first ten years range from 2-3%[3,4,10,14] through 5-6%[5,7-9,12] to 9-10%[2,13], again precluding direct comparisons between estimates. Observed variations in both relative risk and actuarial risk are probably due to differences in both methodology and exposure.

Although cases of leukaemia have been observed after radiotherapy in the absence of chemotherapy for Hodgkin's disease, the magnitude of the risk ratio is much lower, and may not even be elevated[6,19]. In contrast, the risk for ANLL is consistently high after chemotherapy even in the absence of radiation[7-9]. Although few untreated patient-years have been analysed recently, the relative absence of ANLL as an observed sequel of Hodgkin's disease prior to the era of intensive combined regimens[20,21], the absence of any relationship to histological subtype[13], and the appearance of ANLL during complete remission[5] emphasize the etiological role of chemotherapy, although interactions with stage of disease, with radiation or with factors important in the pathogenesis of Hodgkin's disease itself cannot be ruled out completely.

The only specific drug combination that has been used with sufficient frequency that it can be clearly linked to ANLL is MOPP (nitrogen mustard [see p. 269], vincristine [see p. 372], procarbazine [see p. 327] and prednisone [see p. 326]), although several reports describe excess cases not attributable to MOPP[9,11,14,16], and excesses of ANLL have appeared after treatment with other alkylating agent-containing combinations. The predominance of combined chemotherapy also precludes the identification of risk from individual constituents. Preliminary experience does indicate that risk for ANLL may be lower with some specific combinations, such as ABVD (adriamycin, bleomycin, vinblastine and dacarbazine)[14,22,23].

Solid tumours, especially non-Hodgkin's lymphomas[10,24-27] and lung cancer[3,6,12,28,29], but including sarcomas, melanoma, malignancies of the central nervous system and carcinomas of the thyroid and gastrointestinal system, have also been reported in abundance after combined chemotherapy for Hodgkin's disease[3,6,7,10,12,29-32], but comparisons of observed to expected frequencies have not yielded consistent results. In contrast to leukaemia, solid tumours are more common in the general population, increase rapidly in frequency with age (and therefore the passage of time after treatment), are more diverse in

known etiology, and are considered to appear with greater frequency after intensive radiotherapy[6]. Moreover, they are observed to appear with increasing frequency only after longer average duration of follow-up[32]. Some reports have shown increased risk after intensive chemotherapy[10], and the plausibility of a relationship is further suggested by multiple case reports of second malignancies that are unusual because of their rarity, either at an age[33] or on an absolute basis[9,24,31]. At present, it would appear that solid tumours occur among survivors of Hodgkin's disease in excess of the expected frequency; but, because too few patients have been followed into the second decade after treatment, it is too early to determine whether the increase can be better attributed to chance or to factors other than chemotherapy[32].

Combined chemotherapy containing alkylating agents for non-Hodgkin's lymphoma may also lead to ANLL[34-37], although the reports are not consistent and the documentation is less complete.

Treatment of nonhaematological malignancies may also cause second tumours, but most reported cases have occurred after the use of single agents[38], and combination regimens are less commonly used. Intensive combination therapy including alkylating agents for small-cell carcinoma of the lung[39,40], and possibly for cancer of the testis[41], may increase the risk for ANLL.

B. Evidence for carcinogenicity to animals (*inadequate*)

No data on MOPP were available to the Working Group. Combined treatment with cyclophosphamide (see p. 182), methotrexate (see p. 241) and 5-fluorouracil (see p. 210) induced carcinogenic responses in several organs in rats[42]. See also the summaries of data on individual compounds: adriamycin (see p. 81), bleomycins (see p. 134), chlorambucil (see p. 144), cyclophosphamide, 5-fluorouracil, methotrexate, nitrogen mustard (see p. 269), prednisone (see p. 326), procarbazine hydrochloride (see p. 327), vinblastine sulphate (see p. 371) and vincristine sulphate (see p. 372).

C. Other relevant data

For data on genetic and related effects, see the summaries on individual compounds, listed above.

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