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Perspectives in Cancer Research

Treatment of Neoplastic Meningitis

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INCIDENCE

NEOPLASTIC meningitis is characterized by a diffuse or multifocal seeding of the leptomeninges by tumour cells. These neoplastic cells usually originate from extraneural tumours, rarely being secondaries of primary brain tumours such as medulloblastomas or ependymomas. Exceptionally, primary leptomeningeal tumours such as primary melanomatosis or primary glioblastomatosis may occur. In the category of neoplastic meningitides of extraneural origin, we will consider separately the meningeal leukemias and lymphomas that are the most common, and the leptomeningeal metastases of solid tumours (the so-called meningeal carcinomatosis). Among these, breast and lung carcinomas and melanomas figure prominently, although in older series, cancers of the gastrointestinal tract, especially cancer of stomach, were the most common primaries, possibly because of their higher incidence at that time.

The general incidence of neoplastic meningitis is difficult to ascertain due to the differences in the diagnostic criteria used by various authors, such as the inclusion or not of meningeal carcinomatosis associated with parenchymal involvement of the central nervous system, retrospective diagnosis or diagnosis based on clinical ground. The incidence of meningeal leukemia in children with acute lymphoblastic leukemia (ALL) has changed considerably in the last 30 yr, first increasing from 5 to over 50% and then falling to approximately 5% with the systematic use of central nervous system prophylaxis.

In a series of 210 adults with acute or chronic leukemia or non-Hodgkin's lymphomas observed between 1974 and 1978 [1], the incidence of meningeal disease was 33% for patients with acute lymphoblastic leukemia (ALL), 20% for patients with acute myelogenous leukemia (AML), 22% for patients with non-Hodgkin's lymphomas, 3% for patients with chronic myelogenous leukemia (CML) and 1% for patients with chronic lymphocytic leukemia (CLL).

The incidence of meningeal carcinomatosis is largely unknown. In a study performed at the Baltimore City Hospital and John Hopkins Hospital in 1976, 1.3/1000 of all autopsied cases had pure meningeal carcinomatosis as the only manifestation of central nervous system metastases [2].

However, although no precise figure can be given, leptomeningeal metastases are increasingly being recognized as a cause of neurological disability in cancer patients. For example, Nugent *et al.* have reported an increased frequency over time in patients with small cell bronchogenic carcinoma [3].

Breast carcinoma [4] and possibly ovarian carcinoma [5] appear to follow the same trend. In addition to an increased awareness of this complication and an improvement in the diagnostic tools, this increased incidence of meningeal carcinomatosis is due to: (1) the longer survival of some groups of cancer patients, such as oat cells carcinoma of the lung and perhaps ovarian carcinoma, and the higher rate of long survivals in patients with clinical evidence of breast carcinoma; and (2) the fact that systemic chemotherapy does not reach the subarachnoid space in sufficient quantity to achieve cytotoxic levels.

TREATMENT

Treatment of overt meningeal leukemia

Among all neoplastic meningitides, meningeal leukemia was the first to receive an increased attention because it appeared rapidly as a major obstacle to achieve complete remission in

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children with ALL. Nevertheless, the treatment of overt central nervous system leukemia still remains a therapeutic challenge.

The best results in the treatment of overt CNS leukemia have been reported by Bleyer *et al.* with methotrexate (MTX) given via a subcutaneously implanted Omaya reservoir [6]. Two different regimens were compared: 12 mg/m^2 in a single intraventricular injection and the so-called 'concentration × time' regimen consisting of 1 mg of MTX injected every 12 hr 6 times; both regimens are repeated every 4–8 days for 8 weeks and thereafter monthly. The rationale proposed for the fractionated regimen is that it maintains a therapeutic level of MTX within the CSF for 72 hr instead of 23 hr with the single injection of 12 mg/m^2, and therefore exposes more tumour cells in the S phase to MTX. Actually both regimens appear equally effective, but the neurotoxicity is lower with the 'concentration × time' regimen, probably because of the lower peak of CSF MTX and of the reduced cumulative MTX dose.

It is to be noted that this kind of treatment was made possible by the use of the Omaya reservoir, which allows an easier access to the CSF and permits the intraventricular administration of MTX, providing a cytocidal MTX concentration throughout the entire CSF compartment [7, 8].

Other chemotherapeutic agents have also been used for intrathecal injection but appeared less effective, perhaps because of the lack of maintenance therapy in those trials. Wang and Pratt [9] treated 13 patients with meningeal leukemia (11 ALL, 2 AML) with intrathecal cytosine arabinoside (Ara-C) at doses ranging from 5 to 70 mg/m^2 twice a week. Seven patients responded to the treatment, but the mean duration of remission was only 28 days.

Band *et al.* [10] observed an objective clinical improvement in 6 patients with ALL and 3 with AML after the intrathecal administration of 4.5–73 mg/m^2 of Ara-C every 3–7 days, but the CSF blast count was lower than 2/mm^3 in only half of the patients at the end of the treatment.

There have also been some positive reports with thiotepa at doses ranging from 1 to 10 mg/m^2; 3 patients with ALL had a complete response, 4 others had a partial response and 2 failed to respond [11].

More recently, intrathecal interferon was used in the treatment of 5 patients with ALL presenting with isolated meningeal disease. Tolerance was excellent but only one patient had a complete remission, the others showing no improvement after 5–8 injections [12].

Substances that cross the blood–brain barrier have been administered systemically, a route which appears interesting on a physiological basis, with some encouraging results and, although they are not first choice drugs, their use should be considered when intrathecal treatment cannot be used or is no more effective.

Pyrimethamine, a potent folic acid antagonist, was administered to 2 patients with ALL at doses of 2 mg/kg/day for 7 days, repeated every 2–3 months and remissions lasting for more than 7 yr were obtained [13]. These results contrast with a previous report in which only 6 and 7 month remissions were achieved in 2 episodes of meningeal leukemia in a long-term survivor with AML [14].

BCNU was used with some success by Nies *et al.* [15]. More recently, Bleyer *et al.* evaluated the effect of high-dose intravenous MTX infusion in one patient with overt meningeal leukemia [16]. A central nervous system remission was achieved after a single 24-hr infusion consisting of a first dose of 3000 mg/m^2 MTX given during the first hour and 600 mg/m^2 per hour during the subsequent 23 hr. The ventricular CSF MTX level was found to be within the therapeutic range.

Radiotherapy alone was found to be of limited value in overt meningeal leukemia. Craniospinal irradiation with 1000 rad produced a remission of CSF abnormalities in 92% but the mean duration was limited to 52 days [17]. The duration of the remission was later prolonged to 216 days by increasing the dosage of craniospinal irradiation to 2000–2500 rad [18]. However, the benefit of the addition of craniospinal irradiation to the intrathecal administration of methotrexate has been established only when intrathecal chemotherapy is not maintained [19, 20].

In summary, (1) intrathecal MTX produces a high rate of remission (>90%) in patients with overt meningeal leukemia. The maintenance of intrathecal MTX appears mandatory to increase the duration of the remission. Results obtained with other drugs are less satisfactory, perhaps because the maintenance of intrathecal chemotherapy was omitted. Promising results have been achieved with intravenous MTX and pyrimethamine in a few patients, but more comprehensive studies are necessary to evaluate these treatment modalities; (2) craniospinal irradiation alone cannot eradicate an *overt* meningeal leukemia; (3) the benefit of the addition of craniospinal irradiation to the intrathecal administration of MTX has been established only when intrathecal MTX is not maintained.

Prophylactic treatment of meningeal leukemia

The so-called prophylactic treatment of meningeal leukemia was introduced in the management of ALL because a high number of

remissions ended with this complication. This prophylaxis actually aims to eradicate the leukemic seeding of the meninges, which appears to occur early in the development of the disease for the following reasons: (1) two factors which favor the meningeal involvement by lymphoblastic cells, namely a high WBC and low platelet count at the time of diagnosis, have been correlated with the subsequent appearance of meningeal leukemia; (2) the Memphis group showed that a 2- to 3-week CNS treatment applied immediately after complete remission reduces the relapse rate [21]; and (3) Hyman *et al.* [22] observed that CNS leukemia and initial systemic disease have the same sensitivity or resistance to MTX. Yet, intrathecal MTX may still be active in patients whose systemic disease, initially sensitive to MTX, has become resistant to the drug.

The first satisfactory reduction of CNS relapse from 59 to 5% was reported in 1972 by Aur *et al.* after craniospinal irradiation [23]. One year later, the same group confirmed the effectiveness of the irradiation treatment and showed that the combination of cranial irradiation with 2400 rad to 5 intrathecal injections of MTX at doses of 12 mg/m^2 was equivalent in terms of prevention of CNS relapse to a craniospinal irradiation with 2400 rad and was less myelotoxic [21]. More recently, cranial irradiation with 1800 rad associated with 5 injections of intrathecal MTX was shown to be equally effective [24] with probably less neurotoxicity, since several reports suggest that irradiation is the main factor of neurotoxicity after combined therapy [25–27]. Another modality of combined therapy consisting of an intrathecal injection of colloidal radioactive gold (^{198}Au) associated with intrathecal MTX has been used in Jena for the past 10 yr, with a rate of initial CNS relapse of 6.8% [28]. The rationale of the approach proposed by this group is that, since the tumoricide effect is provided by the gamma and mainly the beta rays, which have a limited tissue penetration (3.6 mm), the cerebral parenchyma is less affected than by conventional radiation therapy. Another advantage is that the distribution of the radioactive substance throughout the subarachnoid space can easily be checked by scintigraphic control.

Intrathecal chemotherapy used alone has often been reported to be less active [29]. However, a randomized study performed by the Southwest Oncology Group failed to show any difference in the rate of CNS relapse or in the duration of complete remission in two groups of children with ALL receiving intrathecal MTX with hydrocortisone and Ara-C, associated or not with 2400-rad cranial irradiation [30]. This confirms the previous results of Haghbin, suggesting that irradiation may be omitted in the prophylaxis of CNS leukemia [31]. The difference between these results and the less satisfactory ones reported by other authors [29, 32] may be due to three factors: (1) the early start of CNS prophylaxis during the induction treatment; (2) the intensive systemic chemotherapy including agents such as BCNU, which cross the blood–brain barrier; and (3) the maintenance of a prophylactic treatment for about 3 yr.

The indication for CNS prophylaxis remains more controversial in adults with ALL or other types of acute leukemia, because the risk of CNS infiltration is lower in adults than in children. A recent study of CNS leukemia in adults with ALL has shown that, independently of other risk factors such as an elevated WBC count or an extramedullary invasion, patients under 20 yr of age had a significantly higher risk of CNS involvement [33]. In a review of the literature, Strijckmans and Malarme [34] showed that 11% of all adult patients with acute non-lymphoblastic leukemia (ANLL) in complete remission relapsed in the CNS but that the CNS was the only site of relapse in only 2.6%. In addition, the benefit of CNS prophylaxis in adult acute leukemia has never been clearly demonstrated. A randomized study on the effect of CNS prophylaxis in adults with ALL showed a statistically significant difference in favor of patients who received the prophylaxis, in terms of relapse rate but not in terms of duration of remission or survival [35]. More recently, though, two possible indications of CNS prophylaxis in adults with ANLL seem to emerge from the literature: the first concerns acute monoblastic leukemia, in which CNS infiltration appears to be more frequent than in other ANLL leukemias and where prophylaxis seems effective [36]; the second indication concerns the minority of adult patients with ANLL for whom an eradication of the disease may be expected after total-body irradiation and bone marrow graft.

In summary, (1) the indication for CNS prophylaxis in children with ALL is clear. Most of the recent protocols include cranial irradiation and intrathecal MTX. Promising results have been achieved with intrathecal chemotherapy alone, which is probably less neurotoxic; (2) the benefit of CNS prophylaxis has not been clearly established in adult ALL and is usually omitted in the treatment of adult ANLL. However, this situation may change rapidly if better results are obtained in the treatment of the systemic disease.

Treatment of overt meningeal lymphomas and meningeal carcinomatosis

The therapeutic approach to meningeal lymphoma and meningeal carcinomatosis derives

from the experience gained in the treatment of meningeal leukemia but is less successful.

Most of the protocols for meningeal lymphomas include intrathecal chemotherapy, often associated with radiation therapy, which is usually limited to the cranium to avoid excessive bone marrow toxicity. In the study of Griffin *et al.*, 13 patients with lymphomatous meningitis were treated with intrathecal MTX [37]; 8 also received whole-brain irradiation. Seven patients, most of them treated with combined therapy, improved but all died within 20 months.

Bunn *et al.* treated 14 patients with radiation therapy (3000 rad over 3 weeks) and intrathecal MTX or Ara-C administered twice weekly until the complete disappearance of malignant cells from the CSF and then weekly until the neurological signs and symptoms resolved [38]. In 7 patients with complete response, no subsequent death was attributed to CNS lymphoma.

Intrathecal chemotherapy alone was used by Ziegler and Humming in 28 patients with Burkitt's lymphoma, with a complete response in nearly all patients [39].

Five patients out of 6 with advanced non-Hodgkin's lymphoma and CNS involvement responded to high doses of systemically administered MTX (1–7.5 mg/m^2) plus citrovorum factor. Three had a complete disappearance of the neoplastic cells in the CSF [40].

The response to the treatment of meningeal carcinomatosis was recently analyzed by Wasserström *et al.* in 90 patients. Again the standard treatment consisted of radiation therapy (usually 2400 rad in 8 doses given over 10–14 days) directed to the site of major clinical involvement followed by 5 injections of MTX (7 mg/m^2 twice a week) via an Omaya reservoir [41]. As soon as the CSF cytology improved or clinical stability was achieved, chemotherapy was continued once weekly for as long as the improvement could be maintained. Forty-two patients either stabilized or improved, with a median survival of 8 months in the absence of clear evidence of systemic disease. When considered by category of primary tumor, these results show that patients with breast carcinoma respond better (with 61% of improvements or stabilizations of the clinical status and a median survival of 7.2 months) than those with lung carcinoma (with 39% of clinical improvements or stabilizations and a median survival of 4 months) or with melanoma (where an improvement occurred in 2 patients out of 11, who survived 3 and 6 months). The better results in patients with breast carcinoma are confirmed by Yap *et al.* [42] in their series of 40 cases treated by a combination of whole-brain irradiation (3000 rad over a 2-week period) and intrathecal plus intravenous MTX and citrovorum factor. A complete response was achieved in 26 patients and a partial response in 1 with a median survival of 6 months for the responders and of 1 month only for the non-responders.

In a series of 11 patients with small cell carcinoma of the lung and meningeal carcinomatosis, a relief of the symptoms and an improvement of the neurological signs were obtained in 5 patients after treatment with intrathecal MTX, associated in 2 patients with whole-brain irradiation. All those who responded survived 8 weeks or more, whereas all the non-responders died within 6 weeks [43].

In addition to the primary tumor histology, when the neoplastic meningitis is graded according to the clinical status, retained consciousness appears to be a favorable prognostic factor [44].

Methotrexate is the most widely used drug for intrathecal chemotherapy, but there have also been a few positive reports with Ara-C [45] and thiotepa [46]. Further studies, however, are needed to determine the optimal dose and administration schedule for these drugs and to compare their effectiveness to that of MTX. The possible effectiveness of oral nitrosourea has been suggested by experimental studies in animal models [47] and by isolated clinical observations [48], but this needs further confirmation.

Prophylactic treatment of meningeal lymphoma and meningeal carcinomatosis

The increased incidence of meningeal lymphoma and the high percentage of patients with histological evidence of persistent disease at autopsy despite treatment have led some authors [49, 50] to suggest CNS prophylaxis in patients with histiocytic lymphoma in which CNS complications are particularly frequent. However, no clinical data are available yet to confirm the usefulness of prophylactic treatment in lymphomas.

In other tumours, including breast carcinoma and bronchial oat cell carcinoma, CNS prophylaxis can certainly not be advised at the present time.

SIDE-EFFECTS AND COMPLICATIONS

Radiotherapy

Cranial irradiation may be responsible for nausea and vomiting, usually occurring in the hours following treatment and which can be prevented by corticosteroids [41].

Transient somnolence of varying degrees has been observed during the second month following prophylactic irradiation with 2400 rad, especially in younger children [51]. Steroids improve this

complication and possibly may prevent its occurrence, which also should become less common since the prophylactic irradiation dose is frequently reduced to 1800 rad.

A decrement in intellectual abilities and CT scan changes consisting of an enlargement of the ventricles and sulci and the appearance of hypodense areas within the white matter have also been attributed to cranial irradiation, especially in younger children [52], but for reasons similar to those mentioned for the transient somnolence, this complication is likely to become less common in the future.

Irradiation is also increasingly being considered as a crucial factor in the pathogenesis of disseminated necrotizing leucoencephalopathy characterised by drooling, confusion, irritability, somnolence and coma, eventually leading to death [25, 27]. However, other factors such as high-level systemic methotrexate may play a role in the development of this complication [53].

Abnormally low growth hormone responses to insulin-induced hypoglycemia have been reported as a late complication occurring several months after a prophylactic cranial irradiation with 2400 rad [54].

Irradiation of the entire craniospinal axis is often accompanied by a severe, occasionally lethal, myelotoxicity. It is, however, noteworthy that craniospinal irradiation may reduce the symptoms of the chemical meningitis due to intrathecal MTX [55].

Intrathecal chemotherapy

Aseptic meningitis, characterized by headaches, vomiting, nuchal rigidity and obtundation, is commonly seen within a few hours following the intrathecal injection of methotrexate. The symptoms most often clear within 72 hr and usually do not occur more than once during the course of the treatment [41]. This complication is more common in the treatment of overt meningeal leukemia or carcinomatosis than during the prophylactic treatment, probably because the clearance of MTX is impaired in neoplastic meningitis, thus allowing higher concentrations of CSF MTX, which is the main factor responsible for aseptic meningitis [56].

Despite the use of citrovorum factor, systemic toxicity of MTX may occur and is probably due to the prolonged passage of the intrathecal methotrexate into the blood.

In the series of Wasserström *et al.*, one patient presented acute respiratory symptoms in the hours following the intrathecal instillation of MTX. This may have represented an instance of MTX-induced pneumonitis [41].

Placement and manipulation of the Omaya reservoir

Though rare seizures have been reported [57], the main problem appears to be infection. In a recent review [58], a 13% infection rate is reported, requiring the removal of the reservoir and parenteral antibiotherapy. All the patients had clinical signs or symptoms suggesting infection, and *Staphylococcus epidermidis* was the infecting organism in each case.

Another rare complication is reported by Wasserström *et al.* [41]. In three patients with increased intracranial pressure who were not shunted, ventricular fluid tracked back along the catheter and resulted in large subgaleal collections of CSF that became infected.

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