Multiple Myelomatosis Treated with a Combination of Urethane and an Oral Nitrogen Mustard

By JAMES INNES AND W. D. RIDER

This paper records the results in 17 cases of multiple myelomatosis given oral treatment with urethane and a nitrogen mustard preparation during the period of May, 1951 to January, 1954.

Cases of generalized myeloma usually have hemopoietic depression due to extensive bone marrow involvement and frequently show marked changes in the plasma proteins. Treatment in such cases has always been a major problem, but in recent years a number of chemotherapeutic agents have been tried with interesting but generally disappointing results. Both stilbamidine and urethane have been shown to relieve pain in a proportion of cases, but the use of the former has been largely abandoned because of its frequent damage of the fifth cranial nerve and urethane in effective doses often produces severe nausea. The nitrogen mustards alone appear to have but little influence on the course of the disease and personal experience with their use has confirmed the published reports.

The use of urethane in multiple myelomatosis was first suggested in 1947 by Alvall, and in 1949 Loge and Rundles reported that in four cases treated for 8 to 10 weeks with a daily dosage of 4-6 Gm. urethane, there had been remarkable relief of bone pain with subjective improvement, and that the destructive skeletal lesions appeared to show no radiographic progression over a period of six months. Subsequent reports by other workers have confirmed the improvement that can follow urethane administration in this disease. In general it can be said that at best one half of the patients will derive subjective benefit, and a much smaller proportion will show objective evidence of response, such as correction of anemia and plasma protein aberrations and a fall in blood sedimentation rate. In the occasional case, radiographic evidence of bony healing may occur.

In 1949 Skipper demonstrated a possible synergistic action between urethane and methyl bis (β chloroethyl) amine nitrogen mustard against myeloid chloroleukemia 1394 in mice, without at the same time increase in toxicity. On the basis of this report, it was felt that it would be interesting to try the effect of combined therapy with urethane and a nitrogen mustard in patients with multiple myelomatosis. The nitrogen mustard compound selected was an oral preparation known as R. 151, β-naphthyl-di(2-chloropropyl)-amine, which was supplied by Professor Alexander Haddow of the Chester Beatty Institute, London, and which had been employed in clinical trials in leukemia and allied disorders by the authors since 1950. This drug had been found disappointing when used alone in a series of cases of multiple myeloma. Gelatine capsules containing 25 mg. R. 151 and 0.5 Gm. urethane prepared by Messrs. Boots Pure Drug Co.
TABLE 1.—17 Cases of Multiple Myeloma Treated with Urthane and R. 151

<table>
<thead>
<tr>
<th>Effect</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relief of bone pain</td>
<td>9 of 15 cases</td>
</tr>
<tr>
<td>Fit for return to work</td>
<td>9 of 17 cases</td>
</tr>
<tr>
<td>Anemia</td>
<td>9 improved; 3 no change; 5 deteriorated</td>
</tr>
<tr>
<td>Plasma protein improvement (over 1 gr./100 ml. globulin)</td>
<td>6 of 10 cases. (No data in 6 cases)</td>
</tr>
<tr>
<td>Significant reduction of high B.S.R. (over 30 mm./hr.)</td>
<td>6 of 12 cases</td>
</tr>
<tr>
<td>Radiological evidence of skeletal healing</td>
<td>2 of 17 cases</td>
</tr>
<tr>
<td>Died</td>
<td>11 of 17 cases</td>
</tr>
</tbody>
</table>

Ltd., Nottingham, England proved to be a nonirritating and convenient form of oral therapy. An initial dosage of 2 to 4 capsules daily was well tolerated.

The 17 cases treated were all patients with generalized myelomatosis and, in all but one, confirmation of the diagnosis was obtained by sternal bone marrow examination. In this one case repeated attempts at marrow aspiration proved unsuccessful, but the typical clinical features with progressive anemia, a plasma globulin of 9.3 Gm. per 100 ml., and characteristic radiological findings made the diagnosis reasonably certain. All the patients were considered to have reached a terminal stage of the disease, unsuitable for radiotherapy on account of hemopoietic depression. In six cases where vertebral involvement seemed likely to result in paraplegia, radiation was given to localized areas of the spine.

Three cases showed a local response by radiographic evidence of healing, but this has been discounted in the subsequent assessment. In the remaining 3 cases there was neither relief of pain nor evidence of healing.

In assessing the results, certain criteria were adopted. These were relief of bone pain sufficient to enable a return to the ambulant state, improvement in the degree of anemia and plasma protein changes, and a fall in elevated blood sedimentation rate. Multiple myelomatosis is associated with such a variable survival time that assessment in this respect was felt to be unreliable. Reports of spontaneous remissions occurring in the advanced stages of the disease are very few and not impressive. An analysis of 120 previous cases recorded in the Department of Radiotherapy* confirmed the view that genuine remissions are seldom if ever seen. It was decided therefore to base the assessment of results on the degree of palliation obtained, and while 11 of the 17 patients died during the 32 month period of observation, many showed definite evidence of response.

The results in the 17 cases are shown in table 1.

1. Relief of Bone Pain

This was the most striking subjective improvement obtained and of the 15 patients who had experienced intractable bone pain, 9 were greatly relieved. These 9 patients, who had all been bedridden at the start of treatment, were sufficiently improved in general health to become ambulant and to resume household duties or light work. The case of one man who has been fit for heavy work as a boilermaker for over two years will be described more fully.
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2. Improvement in Anemia

All 17 patients were anemic before treatment was started, the average hemoglobin percentage being 67 (100 per cent = 14.8 Gm. %). In 9 cases with an average initial hemoglobin level of 64 per cent, the average figure after treatment had risen to 89 per cent. Three cases showed little change in hemoglobin values after therapy and in the other 5 progressive deterioration in the blood picture continued unchecked, so that profound anemia was the commonest cause of death.

3. Plasma Protein and Sedimentation Rate Changes

Plasma protein and sedimentation rate estimations were made in all patients before treatment, but in only 10 were complete values obtained at a suitable interval after treatment. All patients with plasma globulin levels over 3.5 Gm. per 100 ml. had sedimentation rates over 100 mm. per hour, but in contrast, three cases having globulin levels under 2.9 Gm. per 100 ml. had sedimentation rates of 110, 62 and 77 mm. per hour. Following treatment there was a general downward trend both in plasma globulins and sedimentation rates in the successful cases. Thus 6 out of 12 cases showed a fall of over 30 mm. per hour in the B.S.R. and in 6 out of 10 cases a reduction of over 1 Gm. per 100 ml. in the plasma globulin was noted. In these six cases the average globulin figures before and after treatment were 6.87 Gm. per 100 ml. and 4.28 Gm. per 100 ml. respectively, while there was an associated rise in the plasma albumin from 2.82 to 3.72 Gm. per 100 ml.

4. Healing of Bony Lesions

Perhaps the most important index of effective treatment in multiple myelomatosis, and that least commonly reported, is radiographic evidence of healing of the characteristic widespread bony lesions. Loge and Rundles in their series of 4 cases treated with urethane, stated that they had found definite evidence of skeletal recalcification in one patient 6 months after the beginning of treatment and Luttgens and Bayrd observed 3 cases where the radiographic improvement was considered of an equivocal nature. The long time required for the recalcification of areas of osteoporosis is probably the reason why bony healing is so rarely seen. Few patients survive long enough. Two cases in the present series, treated for periods of 18 and 22 months have shown definite evidence of recalcification. Figure 1 shows the healing that occurred in the lumbar spine of a man aged 51 years who became ambulant for 12 months after being bedridden with paraplegia for 6 months. He subsequently died of anemia. Figure 2 shows the appearances of the pelvic bones before and 22 months after treatment in the man whose case is reported below. No other patients have shown such unequivocal evidence of bone healing, but in several there has been no obvious radiographic evidence of progress of the disease.

Case Report

The following case is reported because it represents the outstanding response obtained.
A boilermaker aged 60 was admitted to hospital on 20.4.51 with a history of back pain for 4 months and of a recent injury to his ribs. Radiographic examination showed a pathological fracture of his 9th left rib and the typical changes of myelomatosis in the spine, skull and pelvis. His hemoglobin was 78 per cent, R.S.R. 150 mm. per hour, plasma albumin 2.4 Gm. per 100 ml. and globulin 8.1 Gm. per 100 ml. During the first three weeks in hospital his condition deteriorated rapidly with severe bone pains and a fall in hemoglobin to 40 per cent. For 4 weeks he was given oral urethane alone but could not tolerate 6 Gm. daily on account of nausea and vomiting. In spite of blood transfusions he remained anemic and the plasma globulin level rose to 9.5 Gm. per 100 ml. During the next month he was given oral nitrogen mustard alone with no evidence of improvement and further transfusions were required.

Urethane 3 Gm. and R. 151 30 mg. daily were then administered and within one week he felt marked relief of bone pain and his anemia began to improve. After three weeks' treatment he was fit for discharge from the hospital. The dosage was reduced because of leukopenia but he continued to take both drugs until December, 1952, in an average dosage of urethane 1 Gm. and R. 151 50 mg. daily. He was able to return to work in October, 1951 and has remained fit and had been working full time as a riveter until the time of writing. He had pneumonia in January 1952 and sustained a further fractured rib in April, 1952 but recovered quickly from both incidents. The remarkable progress of his blood picture and plasma protein changes during the first year of treatment are shown in figure 3. On 30.1.54 his Hb. was 100 per cent, R.B.C. 4.8 m., platelets 240,000, R.S.R. 20 mm. per hour, albumin 4.31 Gm. per 100 ml., globulin 2.35 Gm. per 100 ml., N.P.N. 33 mg. per 100 ml. Figure 2 shows the bony healing in his pelvis. Similar changes are evident in other bones, but because of great loss in detail which occurs during reproduction, these radiographs are not presented.

TREATMENT

The dosage of urethane and R. 151 has varied considerably both in amount and duration. Most workers reporting beneficial results from urethane in multiple myeloma have employed a dosage of 3 to 6 Gms. daily and have noted frequent nauseating effects in patients taking such large amounts. As stated, the main object of the present trial was to test Skipper's hypothesis that a
Fig. 2: Pelvis before and twenty-two months after treatment in a man aged 60 years.
synergistic action may exist between urethane and nitrogen mustard and accordingly the aim has been to use only small quantities of urethane and nitrogen mustard in the combined treatment. Thus while a few of the earlier cases in the series were given initially 2 Gm. urethane and 100 mg. R. 151 daily, this was the highest combined dosage employed and the daily amounts used for continued administration were only 1 Gm. urethane and 50 mg. R. 151. Previous experience had shown that little benefit could be expected from such small dosage with either of these drugs used alone. The results obtained with the combination would therefore seem to support the suggestion of synergistic action. In none of the patients did nausea demand reduction or cessation of treatment. In the doses used no evidence of undesirable marrow depression was found even when the combined therapy was continued for periods up to 22 months. Routine estimations of the erythrocyte, leucocyte and platelet count were carried out at frequent intervals in all the patients. The terminal anemia was considered to be due to replacement of the bone marrow by myeloma tissue, rather than toxic depression due to the drugs. In the 9 patients whose blood picture improved materially the average duration was 9 months. Repeat bone marrow biopsy was carried out in a few of the cases in an attempt to assess any changes in the myeloma cell infiltration. The results were inconclusive and it is felt that the minute samples of marrow obtained make it most difficult to follow the progress of a disease which is characterized essentially by widely scattered deposits.
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In many of the patients progress was such as to permit treatment to be continued on an outpatient basis. In the absence of sudden or troublesome side effects it was found that visits to hospital at intervals of 4 to 8 weeks for blood and routine examination were sufficiently frequent to allow adequate control of therapy. On an average it was possible to judge which patients were likely to derive benefit within about 6 weeks from starting treatment. In those who did well, maintenance dosage of urethane 1 Gm. and R. 151 mg. daily (1 capsule after food, morning and evening) was carried on for as long as improvement continued.

Summary

1. 17 cases of advanced multiple myelomatosis have been treated with combined chemotherapy using small doses of urethane and an oral preparation of nitrogen mustard.

2. The object of such therapy was to test the hypothesis that a synergistic action existed between these compounds.

3. The results indicate that significant palliation was obtained in many patients treated and that in some the progress of the disease was modified.

4. In the dosage employed such combined therapy appears to be free from undesirable toxic manifestations and suitable for outpatient administration over long periods.

Summary in Interlingua

1. 17 casos de multiple myelomatosis esseva tractate chimotherapeuticamente con un combination de parve doses de urethano e un preparato oral de hydrochlorido de methyl-bis-(beta-chloro-ethyl)amino.

2. Le objectivo del therapia esseva probar le hypothese que il existe un action synergistic del duo compositos.

3. Le resultatos indica que in multes del patientes assi tractate un palliation significative esseva obtenite e que in alicunes le progresso del morbo esseva modificate.

4. In le dosages usate tal therapia combine pare libere de inidesirabile manifestaciones toxic. Illo es usabile in administrationes a longe durantia con patientes visitante.

References

8 Rider, W. D.: Unpublished data.
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