Short report

Multifocal leukoencephalopathy associated with 5-fluorouracil and levamisole adjuvant therapy for colon cancer. A report of two cases and review of the literature

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Summary

Background. Since 1990 the combination of 5-fluorouracil plus levamisole has been considered the standard therapy for stage B2-C resected colon cancer in the adjuvant setting. Since 1992, 14 cases of multifocal leukoencephalopathy following 5-fluorouracil and levamisole therapy have been reported.

Patients and methods. Two cases of this rare but severe neurological syndrome, observed at our Institution within the scope of the INTACC (Intergruppo Nazionale Terapia Adiuvante Colon Carcinoma, Italy) 01 study, are described.

Conclusions. The clinical and radiological features of the syndrome and the relationships between therapy (with the possible pivotal role played by levamisole) and onset of the multifocal leukoencephalopathy are analyzed in light of the literature data.

Key words: adjuvant therapy, colon cancer, multifocal leukoencephalopathy

Introduction

Since 1990, the association of 5-fluorouracil (5-FU) and levamisole (LEV) has been considered the standard adjuvant chemotherapy for stage B2-C resected Colon Carcinoma (CC). The toxicity related to this therapeutic regimen is generally the same as with 5-FU alone [1].

Recently (since 1992), 14 cases of multifocal leukoencephalopathy related to 5-FU/LEV therapy have been reported [2–10]. Since there is no reference in the literature to such an outcome in cases treated with 5-FU alone, it has been suggested that LEV may be a contributory factor. Significantly, an analogous case of multifocal leukoencephalopathy was recently observed in a patient who received adjuvant therapy with LEV alone for melanoma [11].

Two new cases of multifocal leukoencephalopathy, in patients subjected to adjuvant treatment with 5-FU/LEV within the INTACC (Intergruppo Nazionale Terapia Adiuvante Colon Carcinoma, Italy) 01 study, were recently observed at our Institute. Accordingly, in view of the possibility that LEV has a specific role in the pathogenesis of this neurological syndrome, we undertook a review of the literature.

Patients and methods

From March 1992 to February 1995, the INTACC 01 trial enrolled 1827 patients with surgically treated stage B2-C CC. They were treated with 5-FU (450 mg/sm, days 1–5, every 4th week for 6 cycles) and LEV (150 mg, days 1–3, every other week for 24 weeks) or 5-FU and L-leucovorin (370 mg/sm and 100 mg/sm, respectively, on days 1–5, every 4th week for 6 cycles) plus LEV (150 mg, days 1–3, every other week for 24 weeks). Two cases of multifocal demyelinating leukoencephalopathy were observed.

Case 1

V.M., a 60-year-old woman, was given 5-FU/LEV adjuvant chemotherapy after surgery for stage B2 carcinoma of the sigma. The patient had been suffering from depressive syndrome for 14 years and was being treated with tricyclic antidepressants and benzodiazepines; no other concomitant disease was present and she received no other therapy. After the third cycle (10 weeks from start; cumulative dose of LEV, 2.7 g) the patient was referred to the neurological department because of confusional syndrome, aphasia and disorders of behaviour; no fever was present. In the following days, her vigilance level progressively decreased and spasms from decerebration and respiratory distress appeared. A first cerebral TC was negative, while a control TC carried out 2 weeks later showed a widespread hypodensity of hemispheric white matter. The MRI (Figure 1) documented an obvious and widespread hyperintensity of periventricular and hemispheric white matter, with almost symmetrical disposition; similar features were present in cerebellar hemispheres and this result was compatible with multifocal demyelination of possible inflammatory origin. TC and MRI revealed no metastatic lesions.

Results of the serological and liquoral investigations were negative for infection. Two months later, her clinical situation was stable, without specific therapy (and remained unchanged for the next 17 months) with tetraplegia and a need for naso-gastric tube nutrition. No signs of relapse of cancer appeared.

Case 2

B.G., a 54-year-old woman, after surgery, received adjuvant 5-FU/LEV for stage C2 carcinoma of the sigma. She had a history nega-
Figure 1. Case 1 - axial T2-weighted images show extensive white matter abnormalities in a symmetrical fashion, which cause no mass effect.

Figure 2. Case 2 - axial T2-weighted images show bilaterally symmetrical and confluent hyperintensities throughout white matter, mostly affecting the frontal and parieto-occipital subcortical regions. No mass effect is present.

tive for neurological disturbances or other disorders and was receiving no drugs. After the second cycle (6 weeks from the beginning of therapy; cumulative dose of LEV, 1.8 g) she began to manifest behavioural disorders, confusional syndrome, severe ataxia, dysphagia and aphasia, but no fever. She was hospitalized in a neurological department and, after a few days, exhibited neurological impairment requiring sedation with neuroleptics and enteral nutrition with nasogastric tube. The serological and liquoral tests were negative for infection. The gadolinium-DTPA MRI (Figure 2) showed a diffuse and bilateral hyperintensity of hemispheric white matter, with an image compatible with leukencephalopathy but no metastases. After high doses of dexamethasone (DEX) there was a progressive improvement in her symptoms. Six months later the patient still had slight neurological impairment.

Discussion

LEV toxicity is generally mild, even when LEV is used alone, and was negligible in a series of patients in whom it was associated with 5-FU (± leucovorin). The spectrum of side effects (partly dose-dependent) includes myalgia, arthralgia, fatigue, fever, chills, skin rash, nausea, vomiting, anorexia and neurological symptoms. The latter consist mainly of depression, anxiety, insomnia, difficulty in concentration, headache and vertigo. Moertel et al. [1] recorded this neurological symptomatology in 6 (1.3%) of a series of 447 patients affected by CC treated with LEV alone, but none of them were studied with MRI. A demyelinating leukoencephalopathy related to LEV only was documented in animal models and in the above-mentioned case described by Kimmel et al. [11]; in the same report, 3 cases of leukoencephalopathy following tetramisole (a LEV-analogue) therapy were described.

Since 1992, 14 cases of multifocal leukoencephalopathy (other than the cases described in the present report) potentially related to 5-FU/LEV therapy have been published (Table 1). MRI findings were similar in all cases, with evidence of multiple enhancing white-matter lesions with a predilection for periventricular areas. The serological and cerebrospinal fluid investigations excluded an infectious etiology, while the stereotaxic biopsies, performed in 9 cases, showed foci of demyelination with macrophage infiltrates. In all published cases the discontinuation of treatment resulted in a complete normalisation of the neurological picture, while in one patient renewal of therapy with only 5-FU caused no relapse [7]. Not all the patients were treated with DEX, so the indications for use of this therapy remain uncertain. However, in our 2 cases the evolution was unfavourable despite DEX therapy: in the first case, 17 months later, heavy neurological deficits were still present, while in the second, 6 months later, the symptomatology had only partially regressed. It is possible that delayed diagnosis and the beginning of DEX therapy in the first of our cases may have played a role in the unfavourable outcome. On the other hand, in the case reported by Chen et al. [5], neuropathological examination of the brain at the time of autopsy revealed demyelinating lesions that were still immunologically active although clinically quiescent; the MRI findings in the case reported by Critchley et al. [9] were identical.

The appearance of a neurological syndrome during adjuvant therapy with 5-FU/LEV for CC may pose several problems of differential diagnosis; the possibil-
Table 1. Review of reported cases of multifocal leukoencephalopathy related to treatment with 5-FU and LEV.

<table>
<thead>
<tr>
<th>Case [ref.]</th>
<th>Age/sex</th>
<th>Stage*</th>
<th>Weeks of CT</th>
<th>Symptoms at onset</th>
<th>Cerebral biopsy</th>
<th>DEX-therapy</th>
<th>Resolution of symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [2]</td>
<td>68/M</td>
<td>C2</td>
<td>15</td>
<td>Episodes of loss of consciousness</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2 [2]</td>
<td>45/F</td>
<td>C2</td>
<td>18</td>
<td>Confusion, memory loss</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3 [2]</td>
<td>74/F</td>
<td>B2</td>
<td>19</td>
<td>Confusion, slurred speech</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>4 [3]</td>
<td>NR</td>
<td>NR</td>
<td>8</td>
<td>Ataxia, dysarthria, diplopia</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>5 [4]</td>
<td>37/M</td>
<td>B2</td>
<td>14</td>
<td>Confusion, slurred speech, ataxia</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>6 [5]</td>
<td>68/F</td>
<td>C2</td>
<td>8</td>
<td>Lethargy, dysphasia, disorientation</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>7 [6]</td>
<td>51/F</td>
<td>NR</td>
<td>9</td>
<td>Ataxia</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>8 [7]</td>
<td>NR</td>
<td>NR</td>
<td>within 13</td>
<td>Personality change, disorientation</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>9 [7]</td>
<td>NR</td>
<td>NR</td>
<td>&quot;</td>
<td>Focal neurologic signs</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>10 [7]</td>
<td>NR</td>
<td>NR</td>
<td>&quot;</td>
<td>Personality change, seizures</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>11 [8]</td>
<td>57/F</td>
<td>B2</td>
<td>11</td>
<td>Vertigo, ataxia</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>12 [8]</td>
<td>60/F</td>
<td>C2</td>
<td>27</td>
<td>Ataxia, lethargy, headache</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>13 [9]</td>
<td>44/F</td>
<td>C2</td>
<td>16</td>
<td>Seizures, ataxia, memory loss</td>
<td>No</td>
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<td>Yes</td>
</tr>
<tr>
<td>14 [10]</td>
<td>NR</td>
<td>NR</td>
<td>12</td>
<td>Ataxia, left body weakness</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>15 (see text)</td>
<td>60/F</td>
<td>B2</td>
<td>10</td>
<td>Confusion, aphasia, personality change</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>16 (see text)</td>
<td>54/F</td>
<td>C2</td>
<td>6</td>
<td>Confusion, ataxia, aphasia</td>
<td>No</td>
<td>Yes</td>
<td>Partial</td>
</tr>
</tbody>
</table>

LEGEND: CT - chemotherapy, NR - not reported, DEX - dexamethasone.

* Astler-Coller classification.

ity of cerebral metastasis, paraneoplastic manifestations or primary neurological disease, such as multiple sclerosis and viral encephalopathy, must be considered.

The clinical, MRI and histological findings in these two cases do not enable establishment of a clear causal relationship between therapy and encephalopathy. The mechanisms by which 5-FU/LEV therapy could induce a multifocal leukoencephalopathy remain uncertain. Since there are no reports of 5-FU alone causing such a neurological syndrome, the latest investigations have focused on the potential crucial role of LEV. It has been suggested that LEV, an immunologically active drug, could unmask a latent multiple sclerosis, or provoke an anomalous immunological response: the pathological findings of 5-FU/LEV-induced neurological lesions are, in fact, indistinguishable from those of multiple sclerosis or experimental allergic encephalitis. Moreover, hypersensitivity to LEV can induce an inflammatory reaction with cerebral perivascular cuffing by mononuclear cells, as demonstrated in dog models [11]. Some investigators [4, 5] have demonstrated that 5-FU metabolites may be toxic for myelin, so it is possible that LEV might increase 5-FU-induced neurological toxicity, enhancing an immune response to damaged myelin. It has also been demonstrated that LEV can induce immunological vasculitis and specifically inhibit endothelial alkaline phosphatase; this may result in damage to the cerebral capillaries and abnormal functioning of the hematoencephalic barrier, which in turn could lead to the development of an inflammatory leukoencephalopathy in particularly predisposed individuals [6].

It is our opinion that important pathogenic information could be obtained from MRI studies of the subset of patients exhibiting neurological symptoms, even if slight, during therapy with 5-FU/LEV or LEV only; thorough prospective studies in that direction are warranted.

At present, since a clear causal connection is not apparent, it is impossible to evaluate accurately the clinical and statistical relevance of the reported cases in large series of patients given adjuvant chemotherapy for CC. Nevertheless, we recommend that all patients who exhibit neurological symptoms while under treatment with 5-FU and LEV be examined for a multifocal leukoencephalopathy, and that a MRI study of the brain be carried out.

References

8. Ferroir JP, Fenelon G, Beaugerie L et al. Leukoencephalopathy multifocale inflammatoire, complication de la chimio-


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