Prophylaxis of Mucosal Toxicity by Oral Propantheline and Cryotherapy in Children with Malignancies Undergoing Myeloablative Chemo-Radiotherapy

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Mucosal toxicity is an incapacitating complication of intensive chemo-radiotherapy for children with malignant disorders, and is physically and psychologically distressful. It is therefore important to minimize mucosal toxicity in those patients. In this report, the effects of the combined prophylaxis of oral cooling (cryotherapy) and administration of propantheline, an anticholinergic drug, were studied in patients (aged 2-16 year) with acute leukemias or solid tumors, who underwent myeloablative chemo-radiotherapy and autologous peripheral blood stem cell rescue from 1993 to 1997. Patients were pretreated with the combined prophylaxis (n = 12) or single prophylaxis (n = 5), or left untreated (n = 7). The combined prophylaxis significantly reduced the severe mucositis (combined, 8.3%; single, 20.0%; and untreated, 42.9%) and severe diarrhea (combined, 16.7%; single, 60.0%; and untreated, 57.1%). Moreover, the combined prophylaxis tended to shorten the periods of febrile episodes defined as temperature > 38°C (combined, 3.8 days; single, 4.6 days; and untreated, 5.6 days). Therefore, the combination of propantheline and oral cryotherapy may be feasible and effective for reduction of mucosal toxicity in patients with malignancy who undergo high-dose chemotherapy.

propantheline; cryotherapy; mucosal toxicity; peripheral blood stem cell rescue; myeloablative chemotherapy

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Dose escalation of chemotherapy has contributed for improving survival of patients with malignant disorders. Although peripheral blood stem cell (PBSC) rescue has overcome the dose-limitation of anti-cancer drugs, mucosal toxicity has now been focused as a dose-limiting toxicity for cancer treatment. High doses of anti-cancer drugs cause severe mucositis, which not only

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distresses patients with pain but also increases the risk of infection. It is important to minimize mucosal toxicity in children as well as adults, because patients are at higher risk of developing oral mucositis than adults (Sonis and Clark 1991). In attempts to prevent mucosal damage, the efficacy of various agents has been investigated. Among these agents, oral propantheline, anticholinergic drug (Ahmed et al. 1993; Oblon et al. 1997) and oral cooling called cryotherapy (Mahood et al. 1991; Rocke et al. 1993; Cascini et al. 1994; Dumontet et al. 1994; Meloni et al. 1996) have been reported to be effective as sole agents for children. However, to the best of our knowledge, a combination of these two compounds has not been studied yet. Thus, we studied retrospectively whether the combined prophylaxis of propantheline with oral cryotherapy could reduce mucosal toxicity in children with malignant disorders who underwent myeloablative chemo-radiotherapy and autologous PBSC rescue (MCT/PBSC). In this study, we have suggested that the combined prophylaxis may have a beneficial effect to reduce mucosal toxicity that was caused by MCT/PBSC.

Patients and Methods

Patients

Twenty-four children with malignant disorders, 19 males and 5 females, underwent MCT/PBSC from April 1993 to March 1997 in Tohoku University Hospital. Seven patients were with rhabdomyosarcoma (RMS), six with neuroblastoma (NB), three with acute lymphoblastic leukemia (ALL), three with non-Hodgkin’s lymphoma (NHL) and five with each of retinoblastoma, primitive neuroectodermal tumor, undifferentiated sarcoma of the liver, leiomyosarcoma and hepatoblastoma.

Conditioning regimens in MCT/PBSC

We applied several different conditioning regimens according to the disorders. The main two conditioning regimens used were; Hi-MEC regimen with or without pirarubicin for NB, RMS, and other solid tumors consisting of etoposide (200 mg/m² once daily infusion on four days from –7 to –4), carboplatin (400 mg/m² continuous infusion for 24 hrs on four days from –7 to –4), melphalan (60 mg/m² bolus injection three times every 12 hrs on days from –3 to –2), and pirarubicin hydrochloride (40 mg/m² continuous infusion on two days from –7 to –6); MCVAC regimen for ALL and NHL consisting of ranimustine (250 mg/m² infusion on day –8 and 200 mg/m² infusion on days –3), cytarabine (2,000 mg/m² every 12 hrs infusion on four days from –7 to –4), etoposide (200 mg/m² every 12 hrs infusion on four days from –7 to –4), cyclophosphamide (50 mg/m² once daily infusion on two days from –2 to –1). In several cases, there were minor modifications in the conditioning regimens. Melphalan or total body irradiation (2 Gy × 6 = 12 Gy), two of major causes of mucosal toxicity, was used in twenty or four patients, respectively. Three patients received both of TBI and melphalan. The use of these conditioning regimens were approved by the Institutional Review Board.
Evaluation of mucosal toxicity

Pediatric oncologists evaluated the extent of oral mucositis and diarrhea by grading according to the WHO grading criteria. We considered oral mucositis and diarrhea of grade 1 as “mild”, grade 2 as “moderate” and grade 3 and 4 as “severe” toxicity. The state of infectious complication was also evaluated by measuring the periods of febrile episode (> 38°C) and increased C-reactive protein (CRP > 3.0 mg/dl).

Statistical analysis

Mann-Whitney’s U-test was used for statistical evaluation of the incidence and severity of mucositis and diarrhea. Probability values lower than 0.05 were considered significant.

RESULTS

Treatment compliance

The general compliance of the prophylaxis was good in most cases, and most patients were able to take propantheline orally without much problem. However, in some young children who could not stay awake in the evening, cryotherapy was not performed properly.

Mucosal toxicity

The toxicity of oral mucosa of grade 2 (moderate) to grade 4 (severe) was observed 1/12 (8.3%), 3/5 (60.0%), and 5/7 (71.4%) in combined prophylaxis, single prophylaxis, and untreated groups, respectively. Despite the fact that all of the children who received total body irradiation were treated with the combined prophylaxis, all the children except for one case had oral mucositis of grade 1 (mild), whereas severe oral mucositis (grade 3 to 4) was complicated in 20.0% and 42.9% of the single prophylaxis and untreated children, respectively (Table 2). The incidence of severe oral mucositis (grade 3 to 4) was significantly lower in the combined prophylaxis group (8.3%) as compared with that of the other two groups (33.3%) (p = 0.0069). Furthermore, the severe diarrhea was observed
only 2/12 (16.7%) in the combined prophylaxis group, whereas 3/5 (60.0%) and 4/7 (57.1%) in single prophylaxis and untreated groups, respectively. The incidence of severe diarrhea (grade 3 to 4) was also decreased significantly in the combined prophylaxis group as compared with that of the other two groups (58.3%) (p = 0.027) (Table 3). Concerning the five children treated with single prophylaxis, there was no noticeable difference in mucosal toxicity between cryotherapy and propantheline.

**Infectious complications**

On average, the period of febrile episode was 3.8 days (ranged 0-10) in the combined prophylaxis group, 4.6 days (1-9) in single prophylaxis group, and 5.6 days (2-12) in untreated group. Similarly the average period when CRP value was greater than 3 was 5.0 days in combined prophylaxis group, 5.6 days in single prophylaxis group, and 6.1 days in untreated group. Thus, infectious complication evaluated by measuring the periods of febrile episode and increased CRP value was relatively shortened in the combined prophylaxis group as compared to that in the other two groups.

**Clinical course and prophylaxis-related complications**

There was no difference among three groups in hematological recovery, tumor response and

**Table 2. Severity and incidence of oral mucositis.**

<table>
<thead>
<tr>
<th>Prophylaxis</th>
<th>No. of patients</th>
<th>WHO Grade</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Combined (Cry. and Pro.)</td>
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<td>11</td>
</tr>
<tr>
<td>Single (Cry. or Pro.)</td>
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<td>2</td>
</tr>
<tr>
<td>Untreated (None)</td>
<td>7</td>
<td>2</td>
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</table>

Combined, combined prophylaxis group; Single, single prophylaxis group; Untreated, untreated group; Cry., cryotherapy; Pro., propantheline. *The incidence of grade 3 to 4 mucositis was significantly decreased in the group A (p < 0.01) as compared with that of the other two groups.

**Table 3. Severity and incidence of diarrhea.**

<table>
<thead>
<tr>
<th>Prophylaxis</th>
<th>No. of patients</th>
<th>WHO Grade</th>
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<tr>
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<tr>
<td>Combined (Cry. and Pro.)</td>
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<tr>
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</tr>
<tr>
<td>Untreated (None)</td>
<td>7</td>
<td>1</td>
</tr>
</tbody>
</table>

Combined, combined prophylaxis group; Single, single prophylaxis group; Untreated, untreated group; Cry., cryotherapy; Pro., propantheline. *The incidence of grade 3 to 4 diarrhea was decreased significantly in the group A (p < 0.05) as compared with that of the other two groups.
survival rates. Median days after MCT/PBSC at which white blood cell count (WBC) increased more than 1,000/μl was day 10 in all groups. There was no complication that was thought to be associated with propantheline administration and oral cryotherapy.

**DISCUSSION**

In the treatment for patients with malignant disorders, mucosal toxicity is a common and serious complication caused by radiation or chemotherapeutic agents in high doses. When complicated with severe mucosal toxicity, increased risk of bleeding or infection as well as oral and abdominal pain, which may lead to apoclesis, is the major concern for immunosuppressive and myelosuppressive patients undergoing MCT/PBSC. There have been many reports on the decreasing incidence of chemotherapy- or radiation-induced mucosal toxicity by using the agents such as allopurinol (Howell et al. 1981), leaser treatment (Barasch et al. 1995; Wong and Wilderman-Smith 2002), oral glutamine (Skubitz and Anderson 1996), tretinoin cream (Cohen et al. 1997), granulocyte-macrophage colony-stimulating factor (Rosso et al. 1997), recombinant human keratinocyte growth factor (Meropol et al. 2003), and calcium phosphate mouth rinse (Papas et al. 2003). In most cases, however, these methods may not be suitable for younger children and their cost-benefit may not be as good as expected.

On the other hand, there have been several reports on the effective prophylaxis of cryotherapy or propantheline to mucosal toxicity. Oral cryotherapy (Mahood et al. 1991; Rocke et al. 1993; Cascarini et al. 1994; Dumontet et al. 1994; Meloni et al. 1996) reduced the salivary secretion of anticancer agents into the mucosa by the mechanism of a local vasoconstriction. Propantheline (Ahmed et al. 1993; Oblon et al. 1997) is an anticholinergic agent which induced a decreased salivation and, thereby, xerostomia. These treatments are not expensive and not difficult to be applied for children.

We demonstrated that oral cryotherapy combined with administration of propantheline was the treatment with a good compliance even for younger children. Moreover, this combination decreased the incidence as well as severity of mucosal toxicity that was caused by conditioning regimens including melphalan, etoposide or TBI in children with malignant disorders who underwent autologous MCT/PBSC. This combined prophylaxis seemed to have an additive effect through mechanisms that reduce salivation as well as decrease salivary excretion of antineoplastic agents. Furthermore, this prophylaxis not only relieved the pain and discomfort of the patients, but also could have a potential to decrease the risk of infectious complications.

It is difficult to draw a definite conclusion from this study with a limited number of patients, because this was a retrospective study with unbalanced distribution of children. However, there was a significant decrease in the incidence and severity of mucosal toxicity in the combined prophylaxis group of children as compared to that of the other two groups. Therefore, these findings suggest that the combined prophylaxis with propantheline and oral cryotherapy may be effective for reducing the incidence and severity of mucosal toxicity caused by MCT in patients with malignant disorders.

**References**


A. Sato et al.


