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Treatment of high-risk neuroblastoma

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Although high-dose chemotherapy and autologous stem cell transplantation (HDCT/autoSCT) have improved the prognosis for patients with high-risk neuroblastoma (NB), event-free survival rates remain in the range of 30 to 40%, which is unsatisfactory. To further improve outcomes, several clinical trials, including tandem HDCT/autoSCT, high-dose ^{131}I-metaiodobenzylguanidine treatment, and immunotherapy with NB specific antibody, have been undertaken and pilot studies have reported encouraging results. Nonetheless, about half of high-risk NB patients still experience treatment failure and have no realistic chance for cure with conventional treatment options alone after relapse. Therefore, a new modality of treatment is warranted for these patients. In recent years, several groups of investigators have examined the feasibility and effectiveness of reduced-intensity allogeneic stem cell transplantation (RI alloSCT) for the treatment of relapsed/progressed NB. Although a graft-versus-tumor effect has not yet been convincingly demonstrated in the setting of relapsed NB, the strategy of employing RI alloSCT has provided hope that treatment-related mortality will be reduced and a therapeutic benefit will emerge. However, alloSCT for NB is still investigational and there remain many issues to be elucidated in many areas. At present, alloSCT is reserved for specific clinical trials testing the immunomodulatory effect against NB.

Key words: Neuroblastoma, High-dose chemotherapy, Allogeneic stem cell transplantation

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Introduction

Neuroblastoma (NB) is the most common extracranial solid tumor in children. The most important clinical and biologic prognostic factors currently used to determine treatment are the age at diagnosis, stage of disease, *MYCN* amplification status, DNA ploidy, and histology[1-7]. While the prognosis of low- or intermediate-risk NB is excellent with conventional treatment modalities, the prognosis of high-risk NB is very poor with conventional treatment alone[8,9].

Treatment of high-risk NB

A strategy using high-dose chemotherapy and autologous stem cell transplantation (HDCT/autoSCT) has been explored to improve the prognosis of patients with high-risk NB. This strategy is based on the hypothesis that dose escalation might improve the survival of children

with high-risk NB. The results of randomized trials comparing HDCT/autoSCT with chemotherapy alone showed a better event-free survival (EFS) in the HDCT/autoSCT arm than in the continuous chemotherapy arm[9-11]. Thus, HDCT/autoSCT has been the standard consolidation treatment. The current standard treatment for high-risk NB is composed of induction treatment (conventional chemotherapy and surgery with or without radiotherapy), HDCT/autoSCT as a consolidation treatment, and 13-cis-retinoid acid treatment to reduce relapse from minimal residual disease. However, the EFS rates after single HDCT/autoSCT are in the range of 30 to 40%, which is unsatisfactory. In this context, several clinical trials to further improve the survival of high-risk NB patients are under evaluation.

Clinical trials to improve outcome in high-risk NB

1. Tandem HDCT/autoSCT

The main cause of failure after single HDCT/autoSCT is relapse or tumor progression rather than treatment-related mortality. Thus, some investigators have explored the efficacy of double or triple tandem HDCT/autoSCT to further improve the outcome of high-risk NB patients[12-14]. This strategy is based on the hypothesis that further dose escalation might result in further improvement in survival rates. Results from a small number of pilot studies suggest that further dose escalation might result in further improvements in the EFS of these patients. Although the number of studies employing tandem HDCT/autoSCT strategy is limited, long-term EFS rates were around 50 to 60%.

George et al.[12] first carried out a single arm trial of tandem HDCT/autoSCT as consolidation therapy for high-risk NB and reported improved long-term survival (5-year EFS 47%) with acceptable toxicity. Kletzel et al.[13] also conducted a single arm trial of triple tandem HDCT/autoSCT and reported improved survival (3-year EFS 57%). Sung et al.[14] also reported the result of our tandem HDCT/autoSCT protocol for high-risk NB. The 5-year EFS was 62%. The Korean Society of Pediatric Hematology-Oncology retrospectively investigated the efficacy of tandem HDCT/autoSCT compared to single HDCT/autoSCT[15]. Data were analyzed according to the intent-to-treat at diagnosis. As a result, 5-year EFS rate was higher in the tandem HDCT/autoSCT group than in the single HDCT/autoSCT group (51.2% vs. 31.3%, P=0.030).

These studies demonstrated that further dose escalation might result in additional improvements in the EFS of high-risk NB patients. However, there are still a number of clinical issues to be elucidated. Tandem HDCT/autoSCT has been applied to different patients with different pre-HDCT/autoSCT treatment and with different HDCT regimens. In addition, there has been no randomized study to compare the efficacy of tandem HDCT/autoSCT with single HDCT/autoSCT. A randomized trial comparing the efficacy of tandem versus single HDCT/autoSCT strategy is currently underway by the Children's Oncology Group (COG).

Another issue to address in the tandem HDCT/autoSCT strategy is toxicity from the more intense treatment. The tandem HDCT/autoSCT strategy is based on the hypothesis that further dose escalation might result in improvement over single HDCT/autoSCT in the EFS of high-risk NB patients. Encouraging survival rates in a few trials employing the tandem HDCT/autoSCT strategy have been attributed to the intensive treatment protocol. However, intensive treatment can also increase the frequency and severity of various late adverse effects. Indeed, many long-term survivors in these studies had late adverse effects and still needed long-term follow-up for observation of additional late adverse effects, although they have demonstrated acceptable levels of cognitive and developmental function[16]. Dental abnormalities, hearing loss, nephropathy, and short stature have been the most prevalent late adverse effects. These findings suggest that further studies employing new treatment modalities are needed to reduce late adverse effects without jeopardizing the survival rate. Incorporation of high-dose ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) treatment, instead of total body irradiation (TBI), into tandem HDCT/autoSCT, and anti-GD2 treatment after tandem HDCT/autoSCT seem to be possible options.

2. High-dose ^{131}I-MIBG treatment

The use of targeted radionuclides allows the delivery of very large radiation doses to the tumor with less radiation to normal tissue. Targeted radionuclide therapy using MIBG for delivery of radiation in the form of ^{131}I has been used extensively to treat relapsed or refractory NB. Recently, high-dose ^{131}I-MIBG treatment was given with autologous stem cell rescue for the treatment of relapsed and refractory NB. The Children's Cancer Group (CCG) treated relapsed or poor response patients with high-dose ^{131}I-MIBG therapy and stem cell support[17]. About 1/3 of the patients responded. However, the treatment was not enough to prevent tumor progression in most cases. Therefore, recently, investigators have incorporated ^{131}I-MIBG treatment into HDCT/autoSCT[18,19]. This therapy has been feasible and effective at 12 mCi/kg ^{131}I-MIBG, and HDCT doses minimally decreased from those without ^{131}I-MIBG treatment[18]. A phase II study is currently underway for the treatment of newly diagnosed high-risk NB, but not for relapsed tumors. A clinical trial that incorporates high-dose ^{131}I-MIBG treatment, instead of

TBI, into tandem HDCT/autoSCT to reduce late adverse effects without jeopardizing the survival rate is under evaluation at our center. Preliminary results are encouraging. Instead of MIBG, anti-GD2, which is also specific to NB cells, can also be used for targeted radionuclide therapy. Cheung et al.[20] conducted a pilot study of high-dose ^{131}I-(anti-GD2) and stem cell support, and they reported an encouraging result.

3. Immunotherapy

To further improve the outcome of high-risk NB patients, various kind of immunotherapy are now under evaluation. Anti-GD2 treatment after tandem HDCT/autoSCT might also be an option to further improve the outcome. Recently, Yu et al.[21] from COG reported the results of their phase III trial. High-risk NB patients who remained progression free after single HDCT/autoSCT were eligible in this study. Anti-GD2 treatment plus 13-*cis*-retinoic acid treatment after HDCT/autoSCT was superior to 13-*cis*-retinoic acid treatment alone for EFS and overall survival. Interleukin-2 (IL-2) treatment to enhance natural killer (NK) cell activity might be an option after HDCT/autoSCT because NB cells do not express human leukocyte antigen (HLA) class I antigen, and therefore, can be an excellent target for NK cell[22].

Allogeneic SCT after relapse

About half of high-risk NB patients still die from treatment failure even after tandem HDCT/autoSCT. The major cause of treatment failure is tumor relapse. Conventional chemotherapy has been ineffective after relapse in these patients, and they cannot tolerate additional intensive treatment because they had been intensively treated previously. There has been no realistic chance for cure with conventional options alone[23], and therefore, a new modality of treatment is warranted for these patients. In this context, allogeneic SCT (alloSCT) is being investigated as a potential curative treatment option for patients who failed previous HDCT/autoSCT because it offers a graft-versus-tumor (GVT) effect not seen in autoSCT. AlloSCT results in recovery of properly functioning immune cells that can correct any functional defects that exist in their autologous counterparts, which may provide a beneficial GVT effect. The graft-versus-leukemia (GVL) effect is a widely accepted major component of alloSCT in leukemias[24], and there is emerging evidence for a GVT effect in solid tumors[25]. A GVT effect has also been demonstrated in patients with advanced NB who received alloSCT[26-29]. However, regimen-related mortality following standard alloSCT with an intensive conditioning regimen may be extremely high in patients who have already been heavily treated[30-32].

In recent years, several groups of investigators have developed reduced-intensity conditioning regimens that lead to engraftment of donor lymphoid and hematopoietic stem cells without the extra-hematopoietic toxicities of standard myeloablative conditioning, while conserving the GVL or GVT effect. This reduced regimen-related toxicity may make reduced-intensity alloSCT (RI alloSCT) especially suitable for patients at high-risk of regimen-related mortality, particularly previous recipients of tandem HDCT/autoSCT. In adults, striking GVT effects after RI alloSCT have been described in refractory breast cancer and renal cell carcinoma[25]. However, reports concerning the possible GVT effect of RI alloSCT remain very limited in pediatric solid tumors.

Although the number of studies employing RI alloSCT for NB is currently very limited, early studies suggest that this is a feasible approach that has demonstrated GVT effects that were confirmed by the regression of tumor after induction of acute graft-versus-host disease (GVHD) by withdrawal of immunosuppressive drugs or donor leukocyte infusion (DLI). For many years, HLA-matched donors were the only types of donor routinely employed, however, more recently, mismatched SCT has also proved feasible. Jubert et al.[33] applied mismatched cord blood transplantation (CBT) for the treatment of refractory/relapsed NB patients. All patients were in partial response or less than partial response at transplant. CBT was feasible; however, relapse was rapid and there was not enough time to establish a GVT effect in patients with high tumor burden. Haploidentical SCT (haploSCT) also proved to be feasible. In 2003, Inoue et al.[26] first described a boy with refractory NB who received CD34-positive haploSCT after myeloablative conditioning. The tumor ultimately regressed and the authors stressed the possibility of a GVT effect against NB. Lang et al.[27] evaluated the feasibility and toxicity of haploidentical T- and B-cell depleted RI alloSCT with high numbers of NK cells and showed the feasibility and low toxicity of this approach even in intensively pre-treated NB patients. Sung et al.[34] also reported the results of RI alloSCT for NB patients who failed previous tandem HDCT/autoSCT. Regimen-related short-term toxicity was manageable and a GVT effect was observed in 2 of 6 patients after induction of acute GVHD; however, it was not sufficiently strong to control tumor progression in patients who had a significant tumor burden at transplant.

Early studies of RI alloSCT, including haploSCT, suggest that this is a feasible approach. They also demonstrated GVT effect that was confirmed by regression of tumor after induction of acute GVHD. However, the control of GVHD by immunosuppressive drugs resulted in the reemergence of NB. GVT effect was not enough to control tumor proliferation, particularly in patients who had a significant tumor burden at transplant. However, it was difficult to

effectively reduce tumor burden prior to transplant with conventional treatment modalities. Therefore, a new modality of treatment to effectively reduce tumor burden prior to transplant along with post-transplant adjuvant treatment to increase the antitumor effects is needed to improve the outcome after RI alloSCT.

For efficient reduction of tumor burden prior to RI alloSCT without significant toxicity, high-dose ^{131}I-MIBG treatment might be an option because it has no significant toxicity other than hematologic toxicity. Recently, investigators have incorporated high-dose ^{131}I-MIBG treatment into RI alloSCT and demonstrated that it is a feasible approach[35,36]. Another approach is to develop a new salvage treatment regimen with new drugs; however, at present, an effective salvage regimen using new drugs is not available.

Stem cell source is also an important issue to maximize the GVT effect. More GVHD and probably a stronger GVT effect are expected in unrelated or mismatched SCT compared to related or matched SCT. Recently, unrelated or mismatched SCT have also proven to be a feasible approach. Therefore, in a specific subpopulation of patients, unrelated or mismatched SCT might be a preferred option, and not merely an alternative to related or matched SCT. Killer immunoglobulin-like receptor (KIR) ligand mismatched SCT is also a possible option to enhance GVT effect in NB because NB cells do not express HLA class I antigen, and therefore, can be an excellent target for NK cell alloimmunity.

Post-SCT adjuvant treatment to increase the GVT effect might be another approach. DLI or NK cell infusion after SCT and NB specific antibody treatment with or without cytokine treatment might be options to enhance the GVT effect against NB cells. NK cell- or complement-mediated immune response might be more important than T cell-mediated immune response because NB cells generally do not express class I antigen[37].

Different clinical trials employing combinations of the strategies mentioned above are currently under evaluation. For example, Toporski et al.[36] incorporated high-dose ^{131}I-MIBG into haploSCT with T cell depleted graft, and donor leukocytes were infused if GVHD was absent. Lang et al.[27] recently proposed a multicenter study employing an anti-GD2-based immunotherapy combined with haploSCT. They reported that this approach was feasible in their pilot treatment. Pérez-Martínez et al.[37] have recently reported their experience using KIR ligand mismatched haploSCT in 3 refractory metastatic solid tumors including 1 NB. This approach was also feasible and GVT effect was demonstrated. A clinical trial that incorporates high-dose ^{131}I-MIBG treatment into RI alloSCT in patients who failed previous tandem HDCT/autoSCT is under evaluation at Samsung Medical Center. IL-2 infusion is administered if the tumor has progressed or persisted at 6 months after RI alloSCT. Preliminary results are encouraging. At present, we do not know which the best strategy for successful outcome is. Further study will provide an answer.

AlloSCT for newly diagnosed high-risk NB

One of recent approaches for the treatment of newly diagnosed high-risk NB is use of alloSCT. The first alloSCTs for NB were reported in the 1980s and the early 1990s[38,39]. AlloSCT was used as an alternative to autoSCT when autologous bone marrow had not been cleared of tumor or was impossible to harvest, but not really in an attempt to harness an immunotherapeutic effect. Both the CCG[38] and European group[39] reported no difference in relapse between autoSCT and alloSCT, with higher toxic death rate in the alloSCT group. No beneficial antitumor effect of conventional alloSCT was demonstrated and alloSCT was finally, possibly too hastily, largely abandoned in NB treatment for more than 10 years.

Although the initial studies of conventional alloSCT failed to showed clear benefit, interest was recently renewed with the first successful reports of RI alloSCT in solid tumors, and with a few promising experimental studies that demonstrated a measurable antitumor immune response against NB.

Goi et al.[40] evaluated the feasibility of RI CBT following autoSCT in newly diagnosed NB patients. Takahashi et al.[35] also developed a novel SCT protocol to treat newly diagnosed very high-risk NB patients as well as relapsed patients. KIR ligand mismatched CBT is given following autoSCT. This novel protocol is under evaluation in a prospective study. These approaches are based on the hypothesis that immunological effects of alloSCT will be most beneficial in children with minimal tumor burden in their early disease process before relapse.

In summary, the advent of RI alloSCT has provided hope that treatment-related mortality will be reduced and therapeutic benefit will be detected. As an alternative to autoSCT, alloSCT has been studied in an attempt to harness an immunotherapeutic effect. Early studies of alloSCT in children with newly diagnosed high-risk NB suggest that this is a feasible approach that may improve the outcome in this deadly disease. However, alloSCT for newly diagnosed NB is still investigational and there remain many issues to be elucidated in many areas. Therefore, at present, alloSCT is reserved for specific clinical trials testing its immunomodulatory effect, although investigators are beginning to explore the possibility of an allogeneic effect in high-risk NB.

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