

Graft-versus-cancereffect and innovative approaches in the treatment of refractory solid tumors

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Received: 15.11.2019 • Accepted/Published Online: 14.03.2020 • Final Version: 03.11.2020

Background/aim: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has been used for the treatment of various refractory solid tumors during the last two decades. After the demonstration of graft-versus-leukemia (GvL) effect in a leukemic murine model following allo-HSCT from other strains of mice, graft-versus-tumor (GvT) effect in a solid tumor after allo-HSCT has also been reported in a murine model in 1984. Several trials have reported the presence of a GvT effect in patients with various refractory solid tumors, including renal, ovarian and colon cancers, as well as soft tissue sarcomas [1]. The growing data on haploidentical transplants also indicate GvT effect in some pediatric refractory solid tumors. Novel immunotherapy-based treatment modalities aim at inducing an allo-reactivity against the metastatic solid tumor via a GvT effect. Recipient derived immune effector cells (RDICs) in the antitumor reactivity following allo-HSCT have also been considered as an emerging therapy for advanced refractory solid tumors.

Conclusion: This review summarizes the background, rationale, and clinical results of immune-based strategies using GvT effect for the treatment of various metastatic and refractory solid tumors, as well as innovative approaches such as haploidentical HSCT, CAR-T cell therapies and tumor infiltrating lymphocytes (TIL).

Key words: Graft-versus-tumor effect, recipient derived immune effector cells, allogeneic hematopoietic stem cell transplantation, solid tumors

1. Introduction

High dose chemotherapy with autologous hematopoietic stem cell transplantation (HSCT) could not achieve the expected treatment success in patients with solid tumors [2–12]. The ongoing clinical need for more durable responses has led to the search of novel approaches focusing on the graft-versus-tumor (GvT) effect via allogeneic HSCT (allo-HSCT) with reduced intensity conditioning (RIC) and haploidentical HSCT [1, 9–11, 13–18]. Allo-HSCT has been used for the treatment of various refractory solid tumors during the last two decades. GvT effect in a solid tumor after allo-HSCT has also been reported in a murine model in 1984 after the demonstration of graft-versus-leukemia (GvL) effect in a leukemic murine model following allo-HSCT from other strains of mice [19, 20]. Phase I and II trials using allo-HSCT with RIC conducted by the European Society for Blood and Marrow Transplantation Solid Tumors Working Party (EMBT-STWP) have reported the presence of a GvT effect in patients with various refractory solid tumors, including renal, ovarian and colon cancers, as

well as soft tissue sarcomas [1]. The growing data on haploidentical transplants also indicate GvT effect in some pediatric refractory solid tumors [21–25].

The standard chemotherapy-based approaches have been shifting towards immunotherapy-based modalities, which aim at inducing an allo-reactivity against the metastatic solid tumor via a GvT effect [13, 26–33]. The acceptable toxicity profile has enabled allo-HSCT with RIC to be an alternative for the elderly and medically fragile patients with refractory metastatic solid tumors [13, 26]. The evolving evidence has also indicated the potential role of recipient derived immune effector cells (RDICs) in the antitumor reactivity following allo-HSCT, which has been considered as an emerging therapy for advanced refractory solid tumors [1, 34].

This review summarizes the background, rationale, and clinical results of immune-based strategies using GvT effect for the treatment of various metastatic and refractory solid tumors, as well as innovative approaches such as haploidentical HSCT, CAR-T cell therapies and tumor infiltrating lymphocytes (TIL).

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2. Cytotoxic adoptive T-cell therapy

Novel approaches including adoptive T-cell therapy (ATCT), targeted therapies and allo-HSCT with RIC are able to induce more durable responses via the advantage of a GvT effect [1, 13]. Better understanding the mechanisms behind the adoptive immune system has enabled the establishment of new targets for the treatment of various solid tumors [35]. The GvT effect and tumor response after allo-HSCT with RIC depend on the activity and interaction of RDICs, leukocyte-activated killer cells (LAKs) and cytokine-induced killer cells (CIKs). Thus, it may also be regarded as a nonspecific ATCT. ATCT involves the expansion of cytotoxic immune effector cells of either donor or recipient type [36]. According to results of some early phase trials, ATCT may be a potent immunotherapeutic approach in refractory solid tumors [35]. There remains much more to be discovered regarding the interactions of T-cell subsets, mechanisms of GvT effect and differences between GvL effect of hematologic malignancies and GvT effect in refractory solid tumors.

3. Graft-versus-tumor effect

Graft-versus-host disease (GvHD) and therefore GvL effect occurring after allo-HSCT contributes to and maintains an antileukemic feature [37, 38]. Chronic GvHD generally leads to a more potent GvL effect than acute GvHD [39]. The duration of remission is reported to be higher among patients with GvHD when compared to ones without GvHD [40]. Indirect evidences for the presence of an immune-mediated GvL effect include the lower risk of relapse among patients undergoing allo-HSCT when compared to autologous HSCT and an increased risk of relapse among patients receiving T-cell depleted transplants [41, 42]. The direct evidence of GvL effect can be interpreted from the posttransplant studies reporting an augmentation of GvL effect following donor lymphocyte infusions (DLI) after allo-HSCT [43]. DLI without cytotoxic therapy is associated with a high rate and durability of remission when used for the treatment of relapse after allo-HSCT [44–46].

The activation of Fas-dependent killing and perforin degranulation via the GvL effect, which is mediated by donor T-cells (CD4+, CD8+ and natural killer – NK-cells), eradicates malignant cells [47, 48]. Interferon- γ , interleukin-2 and tumor necrosis factor- α are the main cytokines that potentiate the GvL effect [49]. Posttransplant ATCT against human cancer-associated antigens, T-cell receptor genes or minor histocompatibility antigens (e.g.; HA-1, HA-3, etc.) may also induce antitumor effects [50].

The development of acute and chronic GvHD after allo-HSCT, which is an immuno-modulatory therapy aiming at exploiting a GvT effect for solid tumors, has been linked to a better response rate [1]. The identification

of antigen targets of donor and RDICs and development of targeted therapies may further increase the GvT effect of allo-HSCT for solid tumors and also reduce the treatment toxicity [1]. However, the critical balance between effective immunosuppression, GvHD and relapse still remains as a major concern.

3.1. GvT effect in renal cell carcinoma

Although RCC is sensitive to immunotherapy, interferon- α with or without interleukin-2 (IL-2) yields unsatisfactory response (10%–20%) and long-term progression-free survival (PFS) rates of 4%–15% [51–53]. Although the introduction of novel immunotherapeutic agents, such as anti-PDL-1 antibodies (nivolumab and ipilimumab) provided some improvement in overall survival rates of RCC patients, none of the current drugs have a curative potential in RCC [54].

Allo-HSCT with RIC has been considered as a promising option on the basis of GvT effect in this setting [27, 28, 55, 56]. The first series of allo-HSCT with RIC reported a 53% response rate for cytokine-refractory RCC [27]. In the largest series of allo-HSCT with RIC in RCC patients by the EBMT-STWP, in which a fludarabine-based conditioning was administered to all 124 patients, TRM at the end of first year was 16% and mostly associated with acute GvHD [56]. A complete response was achieved in 4 patients at a median of 150 (42–600) days posttransplant with an overall response rate of 22.5%. Another trial with 75 metastatic RCC patients receiving allo-HSCT with RIC reported a sustained engraftment in 74 out of 75 patients [57]. The frequency of chronic GvHD was 50% and associated with a significant tumor response.

As a result, a reasonable GvT effect in RCC patients receiving allo-HSCT with RIC was documented especially in the presence of chronic GvHD, which led to an increase in survival rates.

3.2. GvT effect in refractory and resistant colorectal cancer

The median survival in refractory and resistant colon cancer still remains as low as 9 to 12 months after second-line treatment [58]. The addition of monoclonal antibodies, such as cetuximab or bevacizumab to combination chemotherapies may partially increase remission and survival rates. However, durable remission usually cannot be achieved, especially in the presence of resistant disease [59, 60]. Allo-HSCT with RIC has been studied as an immunotherapy-based therapeutic strategy for the management of metastatic colorectal cancer (mCRC) [15, 16, 61]. Hentschke et al. reported 6 mCRC patients receiving allo-HSCT with RIC, which yielded 1 complete response and 1 mixed response [62]. In a multicenter trial by EBMT, 39 patients with mCRC had allo-HSCT with RIC and all patients engrafted (median donor T-cell chimerism of 90% at day +60). Transplant-related morbidities were limited. Grades II–IV acute GvHD occurred in 14 patients

(35%) and chronic GvHD in 9 (23%). TRM occurred in 4 patients (10%). The best tumor responses were: 1 complete response (CR) (2%), 7 partial response (PR) (18%) and 10 stable disease (SD) (26%), leading to an overall disease control in 18 of 39 patients (46%) [63,64]. The exploitation of GvT effect with allo-HSCT in refractory mCRC might be an alternative to conventional strategies and may sometimes yield favorable outcomes, especially in the presence of chronic GvHD, among young patients with refractory mCRC.

3.3. GvT effect in refractory ovarian cancer

Bay et al. reported 5 refractory ovarian cancer (OC) patients receiving allo-HSCT with RIC. Tumor regression was observed in 4 patients during acute or chronic GvHD and relapse occurred in 1 patient treated with methylprednisolone for chronic GvHD [65]. EBMT-STWP also evaluated 17 heavily pretreated refractory OC patients, retrospectively. Mortality was reported in 11 patients, 8 of whom died of tumor progression at a median follow-up of 296 days (range 51–599) [66]. Grades 2–4 acute GvHD was seen in 8 patients, 7 (41%) of whom had a partial response. DLI was associated with a tumor regression in 1 out of 3 patients. These data support the presence of a GvT effect associated with the severity of GvHD. Another retrospective multicenter study including 30 OC patients receiving allografts reported that the presence of chronic GvHD was associated with a significantly higher overall survival (OS) rate (17.6 months vs. 6.5 months, $P < 0.05$). An objective response rate of 50% and TRM of 20% were reported at the end of first year [67]. Median OS was 10.4 months with a median follow-up of 74.5 months (range 16–148 months).

3.4. GvT effect in breast cancer

Morecki et al. demonstrated a GvT effect in mice implanted with 4T1 mammary carcinoma cell line and given minor histocompatibility mismatched DBA/2 spleen cells [68]. This direct GvT effect mediated by the alloreactive donor splenocytes in the absence of any anticarcinoma agents has also been demonstrated by direct inhibition of liver metastases through intraportal inoculation of allogeneic splenocytes, but not syngeneic splenocytes [69].

The first report of allo-HSCT in metastatic breast cancer (BC) was published by Eibl et al. in 1996 [13]. The advantages of allo-HSCT over autologous HSCT for metastatic BC are i) cancer-free graft and ii) immune-mediated GvT effects mediated by human leukocyte antigen compatible donor T-cells [1, 33, 70]. After the demonstration of tumor regression in metastatic BC via allogeneic T-cell mediated GvT effects in several murine models [71, 72], a study by the National Cancer Institute including 16 metastatic BC patients investigated whether a clinical graft-versus-BC effect existed via allogeneic lymphocytes after allo-HSCT from HLA-matched

siblings following a RIC regimen. In order to avoid the overlap of immunological GvT effect and antitumor effect of cytotoxic chemotherapy used in the pretransplant conditioning regimen, allogeneic T-lymphocytes were removed from the stem cell graft and were subsequently administered at escalating doses after allo-HSCT (on +42, +70, and +98 days). Objective tumor regression occurred in 6 patients 28 days after allo-HSCT. Disease progression following allo-HSCT was observed before subsequent tumor regression in 2 patients. Tumor regressions obtained simultaneously with the accomplishment of complete donor T-lymphoid engraftment were associated with the development of GvHD and abrogated after systemic immunosuppression [32].

A study by Ueno et al. reported that patients who developed acute GvHD after a RIC regimen had lower relapse or progression risk than those who did not ($P < 0.03$). However, this did not translate into a relapse-free survival advantage [33]. Immune manipulation such as DLI for persistent or progressive disease were performed in 9 out of 33 patients (27%) and led to disease response or stable disease. Authors concluded that preclinical and clinical studies are needed in order to facilitate targeted adoptive immunotherapy and to explore the benefit of a GvT effect in BC [33, 36].

3.5. GvT effect in soft tissue sarcomas

Immune-mediated effect against soft tissue sarcomas (STS) has been shown in experimental animal models of allo-HSCT [20, 73]. Most of the evidence comes from case reports and small series of patients transplanted from HLA-matched siblings. Despite several reports of the presence of a graft-versus-sarcoma effect, [74, 75] tumor regression following allo-HSCT with RIC regimens has not been reported among patients with various histologic subtypes [76]. A retrospective study by Secondino et al. evaluated 14 adult patients with advanced STS receiving allo-HSCT with RIC in the EBMT database. Overall, acute GvHD was reported in 9 patients (64%). Grades 3–4 acute GvHD was observed in 4 (28%) and grade 2 in 5 cases (36%). Chronic GvHD occurred in 4 out of 9 evaluable patients (44%) and was extensive in 2. Four patients experienced durable disease stabilization following allo-HSCT [77]. A well designed phase 2 study, enrolling patients with limited tumor burden and slow growing tumors, may help to define the possible role of allo-HSCT with RIC in patients with STS in whom conventional treatments have failed.

3.6. GvT effect of haploidentical stem cell transplantation in refractory solid tumors

Innovative allo-HSCT approaches such as haploidentical HSCT, which takes advantage of GvT effects in order to control disease, while minimizing the treatment related mortality or scale of GvHD, are being studied in many recent clinical trials [21–24]. The evidence of haploidentical

HSCT in solid tumors are mainly limited to pediatric solid tumors such as neuroblastoma and sarcomas [21–23]. A pilot study by Lang et al. evaluated the feasibility and toxicity of transplantation of haploidentical T and B-cell depleted grafts with high numbers of NK cells. Since grade 2 acute GvHD was observed in 4 patients and chronic GvHD in 2, it was concluded that haploidentical HSCT is feasible with low toxicity even in intensively pretreated patients with neuroblastomas and sarcomas [21]. Llosa et al. also reported the results of haploidentical stem cell transplantation with RIC in 16 pediatric and adolescent, as well as young adult patients with solid tumors. A limited GvHD was seen in 3 patients and non-relapse mortality in 1 patient. This approach may serve as a platform for posttransplant strategies to prevent relapse and optimize PFS [22].

4. The role of recipient derived immune effector cells in the antitumor effects

The anticancer effect of RDICs was first time suggested by Alexander et al. in 1996. They reported that xenogeneic lymphocytes from tumor immunized sheep reduced fibrosarcoma growth in immuno competent rats. The observed anticancer effect was not mediated via direct antitumor activity of donor T-cells as these were rapidly rejected in the xenogeneic setting, rather a “messengersignal” created by the infused xenogeneic donor cells in directly boosted recipient’s immune reactions [78]. Ellman and Katz et al. also suggested that host ant-tumor immunity is involved in the antitumor effect [79]. They reported that host antitumor immunity could be achieved even when the all ogenic cells are already fully rejected and continuous tumor protection had been observed in 50% of rechallenged long-term survivors of allogeneic lymphocyte-infused animals [80]. These initial findings suggest that a GvH reaction is a prerequisite for a host-anti tumor activity to occur in the setting of DLI, where RDICs are stimulated to elicit antitumor responses. In concordance, RDICs are presented as key players in the anticancer activity after allo-HSCT. Symons et al. reported that the transfer of CD8+ T-cell-depleted DLI graft into cyclophosphamide-treated A20 leukemia/lymphoma-bearing mice increased the survival directly through a GvH anti-tumor reaction of donor CD4+ T-cells and indirectly through stimulation of recipient CD8+ T-cell antitumor immunity [81].

Recipient derived antigen presenting cells (APCs) also play an important role during GvH reactions. In the early postallo-HSCT period, conditioning-induced tissue inflammation stimulates recipient APCs and they in turn prime alloreactive donor T-cells [82, 83]. Cross-presentation of recipient antigens by donor APCs may also occur after allo-HSCT. However, it still not clearly defined

to what extent it occurs in human beings [83]. The role of recipient APCs in eliciting effective anticancer responses is very important and it is reflected in clinical studies reporting the outcome of DLI in advanced solid tumors. RDICs may have a principal effector role in the anticancer effect against renal cell carcinoma (RCC), as a significant tumor regression occurred despite a gradual decrease in donor chimerism [84]. This observation, reported by Harano et al., suggests that a temporary presence of donor cells is enough to create a GvH reaction and may provide inflammatory signals that facilitate the loss of tolerance of recipient CD8+ T-cells to the recipient’s tumor [84]. Similarly, Omazic et al. also showed a durable remission among patients with advanced refractory solid tumors in the presence of donor graft rejection [37].

As the preclinical and clinical evidences suggest that donor cells may only be needed in the initial induction phase of a GvT effect [37, 81], the research has focused on exploiting the potential of RDICs without increasing the risk of GvHD. In mouse models of leukemia, Rubio et al. and De Somer et al. intentionally created graft rejection via “recipient leukocyte infusion” (RLI) [85, 86]. A host-versus-graft (HvG) reaction created by RLI into mixed chimera as triggered a reaction of RLI-derived donor-reactive recipient T-cells and resulted in full donor graft rejection and an important antileukemic response without increasing the GvHD risk.

In summary, these findings support the initial reports suggesting that RDICs may act as key effectors in the anticancer effect after allo-HSCT. These results also strongly suggest that the effective anticancer responses mediated by RDICs are not solely through a GvH reaction [81, 84], but also a HvG reaction [81, 84, 87, 88].

5. Chimeric antigen receptor T-cell (CAR-T) therapy for solid tumors

Chimeric antigen receptor modified T-cell (CAR-T) therapy has achieved encouraging breakthroughs in the treatment of hematological malignancies. Nevertheless, this success has not yet been extrapolated to solid tumors [89]. In fact, the vast majority of cancers, in particular the more common solid cancers, including the breast, colon and lung, failed to respond significantly to CAR-T treatment. The suppression of T-cell function and inhibition of T-cell localization are some formidable barriers of solid cancers to adoptive cell transfer [90].

However, some promising results have also been reported in some early phase studies [91]. Phase I studies of GD2-specific CAR-T cells for neuroblastoma, CAR-T cells specifically targeting HER2, EGFR and IL-13 for glioblastoma multiforme, mesothelin-specific CAR-T cells for advanced malignant pleural mesothelioma or pancreatic cancer, CAR-T cells specific for epidermal

growth factor receptor (EGFR) for advanced nonsmall-cell lung cancer and cholangiocarcinoma, CEA specific CAR-T cells for metastatic CRC have reported positive initial results [92–99].

Despite some promising results, the ultimate success of CAR-T therapies in solid tumors may require some adjustments and improvements. The combination of CAR-T cells with chemotherapy to treat metastatic tumors, local delivery of CAR-T cells, using CAR-T cells targeting two different antigens, combined therapy with CAR-T and immune check point inhibitors and finally the use of CAR-T as a strategy to prevent tumor recurrence and metastasis after curative resection are current questions to be further studied [89].

6. Tumor infiltrating T-cells in refractory solid tumors

The infiltration of the tumor tissue with T cells targeting tumor associated antigens has been shown to be associated with a favorable prognosis in several solid tumors. Upon this observation ongoing studies have been investigating the idea of extraction, ex vivo expansion with homeostatic cytokines and reinfusion into the patients as a novel treatment strategy [91]. Tumor infiltrating lymphocytes (TILs) were first reported by Rosenberg et al. in 1988 and they demonstrated the antimelanoma effects of IL-2 induced TILs [100]. The treatment with TILs and high-dose IL-2 has proven a 34% objective response rate [101–103]. TIL therapy has been reported to have lower response rates in patients progressed on anti-PD-1 therapy. However, TIL therapy remains an important treatment strategy in refractory malignant melanoma, as durable complete responses can still be induced after progression on anti-PD-1 [104].

Despite the demonstration of TILs in other solid tumors, their expansion and in vivo efficacy have not been a great success as in melanoma [101]. However, there are promising preliminary data with cholangiocarcinoma and cervical cancer [105, 106] and some clinical trials in gastrointestinal, gynecological, head and neck, breast and lung cancers are currently ongoing [91].

TIL therapy in melanoma is an advanced therapy medicinal product and its clinical implementation is challenging. Thus, it has not been widely recognized. It has been available in the Europe since 2011 as an experimental therapy. Reimbursement procedures and organization of knowledge transfer could improve clinical translation of TIL therapy [107].

7. Summary

Current evidence suggests the presence of graft-versus-cancer effect in various solid tumors. Allo-HSCT with RIC may provide some degree of response in some refractory metastatic solid tumors, such as renal, ovarian,

breast and even colon cancers. Lower toxicity profile and lower nonrelapse mortality rate make RIC regimens a plausible treatment modality. To date, the results of this treatment modality in refractory solid tumors are associated with lower CR and PR rates with few long-term survivors, which is similar to CAR-T Cell experiences in refractory solid tumors. Current literature data imply that mechanisms of GvT effect and interaction of T-cells and their subsets with main mediators may be highly different in solid tumors compared to hematologic malignancies. Therefore, further studies are needed shedding light upon these mechanisms in order to exploit this valuable effect in refractory solid tumors.

Despite its great potential, the use of ATCT for cancer control yet has a marginal role in the management of patients with solid tumors. However, it has recently come into attraction in melanoma treatment [36]. Indeed, the extensive infrastructure needed for exploiting ATCT effects still restrict its use to academic centers with specific programs in the field. It should be emphasized that the major obstacle for a wider application of ATCT to treat human cancer is the personalized nature of the approach [36].

Although donor T-cells are accepted as the main mediators of the anticancer effect following allo-HSCT, recent findings also point out a key role for RDICs. Recent experimental studies appointed RLI as an important tool to reinforce anticancer effects after allo-HSCT by exploiting RDICs, both in leukemia and solid tumor models with an advantage of lower rates of GvHD. These results supporting the contribution of RDICs in the anticancer effect of allo-HSCT are mainly observed in murine models, and the experience in human is limited. Future clinical trials may explore the emerging role and anticancer effects of RDICs in patients receiving allo-HSCT.

Further studies and experience are warranted regarding the use of haploidentical HSCT, CAR-T cell therapies, posttransplant immunomodulatory agents and tumor infiltrating T-cells in patients with refractory solid tumors [89, 90, 108–114]. Future studies should include patients with better performance status and chemotherapy responsive disease before transplant in order to obtain the maximal benefit from GvT effect in solid tumors. Well-designed trials are needed for a clear-cut understanding of the interactions of donor T-cells and their subsets, mechanisms of GvT effects, which possibly use different mechanisms in solid tumors and hematologic malignancies, in order to optimize the efficacy of such treatment modalities in patients with refractory solid tumors.

Acknowledgement/Disclaimers/Conflict of interest

Authors have no conflict of interest to disclose.

References

- Demirer T, Barkholt L, Blaise D, Pedrazzoli P, Aglietta M et al. Transplantation of allogeneic hematopoietic stem cells: an emerging treatment modality for solid tumors. *Nature Clinical Practice Oncology* 2008; 5(5): 256-267. Epub 2008/04/10. doi: 10.1038/ncponc1104
- Kroger N, Damon L, Zander AR, Wandt H, Derigs G et al. Secondary acute leukemia following mitoxantrone-based high-dose chemotherapy for primary breast cancer patients. *Bone Marrow Transplantation* 2003; 32 (12): 1153-1157. doi: 10.1038/sj.bmt.1704291
- De Giorgi U, Rosti G, Slavin S, Yaniv I, Harousseau JL et al. Salvage high-dose chemotherapy for children with extragonadal germ-cell tumours. *British Journal of Cancer* 2005; 9 3(4): 412-417. doi: 10.1038/sj.bjc.6602724
- Pedrazzoli P, Ferrante P, Kulekci A, Schiavo R, De Giorgi U et al. Autologous hematopoietic stem cell transplantation for breast cancer in Europe: critical evaluation of data from the European Group for Blood and Marrow Transplantation (EBMT) Registry 1990-1999. *Bone Marrow Transplantation* 2003; 32 (5): 489-494. doi: 10.1038/sj.bmt.1704153
- Demirer T, Gooley T, Buckner CD, Petersen FB, Lilleby K et al. Influence of total nucleated cell dose from marrow harvests on outcome in patients with acute myelogenous leukemia undergoing autologous transplantation. *Bone Marrow Transplantation* 1995; 15 (6): 907-913
- Ladenstein R, Potschger U, Hartman O, Pearson AD, Klingebiel T et al. 28 years of high-dose therapy and SCT for neuroblastoma in Europe: lessons from more than 4000 procedures. *Bone Marrow Transplantation* 2008; 41 Suppl 2: S118-127. doi: 10.1038/bmt.2008.69
- Gratwohl A, Baldomero H, Demirer T, Rosti G, Dini G et al. Hematopoietic stem cell transplantation for solid tumors in Europe. *Annals of Oncology* 2004; 15 (4): 653-660. doi: 10.1093/annonc/mdh142
- Bensinger WI, Demirer T, Buckner CD, Appelbaum FR, Storb R et al. Syngeneic marrow transplantation in patients with multiple myeloma. *Bone Marrow Transplantation* 1996; 18 (3): 527-531.
- De Giorgi U, Demirer T, Wandt H, Taverna C, Siegert W et al. Second-line high-dose chemotherapy in patients with mediastinal and retroperitoneal primary non-seminomatous germ cell tumors: the EBMT experience. *Annals of Oncology* 2005; 16(1): 146-151. doi: 10.1093/annonc/mdi017
- Brunvand MW, Bensinger WI, Soll E, Weaver CH, Rowley SD et al. High-dose fractionated total-body irradiation, etoposide and cyclophosphamide for treatment of malignant lymphoma: comparison of autologous bone marrow and peripheral blood stem cells. *Bone Marrow Transplantation* 1996; 18 (1): 131-141.
- Demirer T, Buckner CD, Appelbaum FR, Clift R, Storb R et al. High-dose busulfan and cyclophosphamide followed by autologous transplantation in patients with advanced breast cancer. *Bone Marrow Transplantation* 1996; 17 (5): 769-774.
- Demirer T, Celebi H, Arat M, Ustun C, Demirer S et al. Autoimmune thrombocytopenia in a patient with small cell lung cancer developing after chemotherapy and resolving following autologous peripheral blood stem cell transplantation. *Bone Marrow Transplantation* 1999; 24 (3): 335-337. doi: 10.1038/sj.bmt.1701902
- Eibl B, Schwaighofer H, Nachbaur D, Marth C, Gachter A et al. Evidence for a graft-versus-tumor effect in a patient treated with marrow ablative chemotherapy and allogeneic bone marrow transplantation for breast cancer. *Blood* 1996; 88 (4): 1501-1508.
- Holmberg LA, Demirer T, Rowley S, Buckner CD, Goodman G et al. High-dose busulfan, melphalan and thiotepa followed by autologous peripheral blood stem cell (PBSC) rescue in patients with advanced stage III/IV ovarian cancer. *Bone Marrow Transplantation* 1998; 22 (7): 651-659. doi: 10.1038/sj.bmt.1701398
- McSweeney PA, Niederwieser D, Shizuru JA, Sandmaier BM, Molina AJ et al. Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose cytotoxic therapy with graft-versus-tumor effects. *Blood* 2001; 97 (11): 3390-3400. Epub 2001/05/23. doi: 10.1182/blood.v97.11.3390
- Slavin S, Nagler A, Naparstek E, Kapelushnik Y, Aker M et al. Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and nonmalignant hematologic diseases. *Blood* 1998; 91 (3): 756-763. Epub 1998/02/03.
- Berry DA, Ueno NT, Johnson MM, Lei X, Caputo J et al. High-dose chemotherapy with autologous hematopoietic stem-cell transplantation in metastatic breast cancer: overview of six randomized trials. *Journal of Clinical Oncology* 2011; 29 (24): 3224-3231. doi: 10.1200/JCO.2010.32.5936
- Pedrazzoli P, Ledermann JA, Lotz JP, Leyvraz S, Aglietta M et al. High dose chemotherapy with autologous hematopoietic stem cell support for solid tumors other than breast cancer in adults. *Annals of Oncology* 2006; 17 (10): 1479-1488. doi: 10.1093/annonc/mdl044
- Barnes DW, Corp MJ, Loutit JF, Neal FE. Treatment of murine leukaemia with X rays and homologous bone marrow; preliminary communication. *British Medical Journal* 1956; 2 (4993): 626-627. Epub 1956/09/15.
- Moscovitch M, Slavin S. Anti-tumor effects of allogeneic bone marrow transplantation in (NZB X NZW)F1 hybrids with spontaneous lymphosarcoma. *Journal of Immunology* 1984; 132 (2): 997-1000. Epub 1984/02/01.
- Lang P, Pfeiffer M, Muller I, Schumm M, Ebinger M et al. Haploidentical stem cell transplantation in patients with pediatric solid tumors: preliminary results of a pilot study and analysis of graft versus tumor effects. *Klinische Pädiatrie* 2006; 218 (6): 321-326. Epub 2006/11/03. doi: 10.1055/s-2006-942256

22. Llosa NJ, Cooke KR, Chen AR, Gamper CJ, Klein OR et al. Reduced-intensity haploidentical bone marrow transplantation with post-transplant cyclophosphamide for solid tumors in pediatric and young adult patients. *Biology of Blood and Marrow Transplantation* 2017; 23 (12): 2127-2136. Epub 2017/08/16. doi: 10.1016/j.bbmt.2017.08.012
23. Kanold J, Paillard C, Tchirkov A, Merlin E, Marabelle A et al. Allogeneic or haploidentical HSCT for refractory or relapsed solid tumors in children: toward a neuroblastoma model. *Bone Marrow Transplantation* 2008; 42 Suppl 2: S25-30. Epub 2008/11/26. doi: 10.1038/bmt.2008.279
24. Sahin U, Demirer T. Future Perspectives for Haploidentical SCT. In: Demirer T, editor. *Haploidentical Stem Cell Transplantation: An Emerging Treatment Modality*: Humana Press, Cham; 2017. pp. 189-199.
25. Zecca M, Comoli P. Applications of Haploidentical SCT in Pediatric Patients. In: Demirer T, editor. *Haploidentical Cell Transplantation: An Emerging Treatment Modality*. Stem Cell Biology and Regenerative Medicine: Humana Press, Cham; 2017. pp. 149-178.
26. Ueno NT, Rondon G, Mirza NQ, Geisler DK, Anderlini P et al. Allogeneic peripheral-blood progenitor-cell transplantation for poor-risk patients with metastatic breast cancer. *Journal of Clinical Oncology* 1998; 16 (3): 986-993. doi: 10.1200/JCO.1998.16.3.986
27. Childs R, Chernoff A, Contentin N, Bahceci E, Schrumpp D et al. Regression of metastatic renal-cell carcinoma after nonmyeloablative allogeneic peripheral-blood stem-cell transplantation. *New England Journal of Medicine* 2000; 343 (11): 750-758. doi: 10.1056/NEJM200009143431101
28. Bregni M, Doderio A, Peccatori J, Pescarollo A, Bernardi M et al. Nonmyeloablative conditioning followed by hematopoietic cell allografting and donor lymphocyte infusions for patients with metastatic renal and breast cancer. *Blood* 2002; 99 (11): 4234-4236. doi: 10.1182/blood.v99.11.4234
29. Carella AM, Beltrami G, Lerma E, Cavaliere M, Corsetti MT. Combined use of autografting and non-myeloablative allografting for the treatment of hematologic malignancies and metastatic breast cancer. *Cancer Treatment and Research* 2002; 110:101-112. doi: 10.1007/978-1-4615-0919-6_5.
30. Ueno NT, Cheng YC, Rondon G, Tannir NM, Gajewski JL et al. Rapid induction of complete donor chimerism by the use of a reduced-intensity conditioning regimen composed of fludarabine and melphalan in allogeneic stem cell transplantation for metastatic solid tumors. *Blood* 2003; 102 (10): 3829-3836. doi: 10.1182/blood-2003-04-1022
31. Blaise D, Bay JO, Faucher C, Michallet M, Boiron JM et al. Reduced-intensity preparative regimen and allogeneic stem cell transplantation for advanced solid tumors. *Blood* 2004; 103 (2): 435-441. doi: 10.1182/blood-2003-07-2236
32. Bishop MR, Fowler DH, Marchigiani D, Castro K, Kasten-Sportes C et al. Allogeneic lymphocytes induce tumor regression of advanced metastatic breast cancer. *Journal of Clinical Oncology* 2004; 22 (19): 3886-3892. doi: 10.1200/JCO.2004.01.127
33. Ueno NT, Rizzo JD, Demirer T, Cheng YC, Hegenbart U et al. Allogeneic hematopoietic cell transplantation for metastatic breast cancer. *Bone Marrow Transplantation* 2008; 41 (6): 537-545. doi: 10.1038/sj.bmt.1705940
34. Dierckx de Casterle I, Billiau AD, Sprangers B. Recipient and donor cells in the graft-versus-solid tumor effect: It takes two to tango. *Blood Reviews* 2018; 32 (6): 449-456. doi: 10.1016/j.blre.2018.04.002
35. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011; 144 (5): 646-674. Epub 2011/03/08. doi: 10.1016/j.cell.2011.02.013
36. Pedrazzoli P, Comoli P, Montagna D, Demirer T, Bregni M et al. Is adoptive T-cell therapy for solid tumors coming of age? *Bone Marrow Transplantation* 2012; 47 (8): 1013-1019. doi: 10.1038/bmt.2011.155
37. Omazic B, Remberger M, Barkholt L, Soderdahl G, Potacova Z et al. Long-Term Follow-Up of Allogeneic Hematopoietic Stem Cell Transplantation for Solid Cancer. *Biology of Blood and Marrow Transplantation* 2016; 22 (4): 676-681. Epub 2016/01/08. doi: 10.1016/j.bbmt.2015.12.017
38. Odom LF, August CS, Githens JH, Humbert JR, Morse H et al. Remission of relapsed leukaemia during a graft-versus-host reaction. A "graft-versus-leukaemia reaction" in man? *The Lancet* 1978; 2 (8089): 537-540. Epub 1978/09/09.
39. Weiden PL, Sullivan KM, Flournoy N, Storb R, Thomas ED. Antileukemic effect of chronic graft-versus-host disease: contribution to improved survival after allogeneic marrow transplantation. *New England Journal of Medicine* 1981; 304 (25): 1529-1533. Epub 1981/06/18. doi: 10.1056/nejm198106183042507
40. Weiden PL, Flournoy N, Thomas ED, Prentice R, Fefer A et al. Antileukemic effect of graft-versus-host disease in human recipients of allogeneic-marrow grafts. *New England Journal of Medicine* 1979; 300 (19): 1068-1073. Epub 1979/05/10. doi: 10.1056/nejm197905103001902
41. Marmont AM, Horowitz MM, Gale RP, Sobocinski K, Ash RC et al. T-cell depletion of HLA-identical transplants in leukemia. *Blood* 1991; 78 (8): 2120-2130.
42. Horowitz MM, Gale RP, Sondel PM, Goldman JM, Kersey J et al. Graft-versus-leukemia reactions after bone marrow transplantation. *Blood* 1990; 75(3): 555-562.
43. Kolb HJ, Mittermuller J, Clemm C, Holler E, Ledderose G et al. Donor leukocyte transfusions for treatment of recurrent chronic myelogenous leukemia in marrow transplant patients. *Blood* 1990; 76 (12): 2462-2465. Epub 1990/12/15.
44. Kolb HJ, Schattenberg A, Goldman JM, Hertenstein B, Jacobsen N et al. Graft-versus-leukemia effect of donor lymphocyte transfusions in marrow grafted patients. *Blood* 1995; 86 (5): 2041-2050. Epub 1995/09/01.
45. Mackinnon S, Papadopoulos EB, Carabasi MH, Reich L, Collins NH et al. Adoptive immunotherapy evaluating escalating doses of donor leukocytes for relapse of chronic myeloid leukemia after bone marrow transplantation: separation of graft-versus-leukemia responses from graft-versus-host disease. *Blood* 1995; 86 (4): 1261-1268. Epub 1995/08/15.

46. Porter DL, Roth MS, Lee SJ, McGarigle C, Ferrara JL et al. Adoptive immunotherapy with donor mononuclear cell infusions to treat relapse of acute leukemia or myelodysplasia after allogeneic bone marrow transplantation. *Bone Marrow Transplantation* 1996; 18 (5): 975-980. Epub 1996/11/01.
47. Hsieh MH, Korngold R. Differential use of FasL- and perforin-mediated cytolytic mechanisms by T-cell subsets involved in graft-versus-myeloid leukemia responses. *Blood* 2000; 96 (3): 1047-1055.
48. Chakraverty R, Eom HS, Sachs J, Buchli J, Cotter P et al. Host MHC class II+ antigen-presenting cells and CD4 cells are required for CD8-mediated graft-versus-leukemia responses following delayed donor leukocyte infusions. *Blood* 2006; 108 (6): 2106-2113. doi: 10.1182/blood-2006-03-007427
49. Schmaltz C, Alpdogan O, Muriglian SJ, Kappel BJ, Rotolo JA et al. Donor T cell-derived TNF is required for graft-versus-host disease and graft-versus-tumor activity after bone marrow transplantation. *Blood* 2003; 101 (6): 2440-2445. Epub 2002/11/09. doi: 10.1182/blood-2002-07-2109
50. Ringden O, Karlsson H, Olsson R, Omazic B, Uhlin M. The allogeneic graft-versus-cancer effect. *British Journal of Haematology* 2009; 147 (5): 614-633. Epub 2009/09/09. doi: 10.1111/j.1365-2141.2009.07886.x
51. Leibovich BC, Han KR, Bui MH, Pantuck AJ, Dorey FJ et al. Scoring algorithm to predict survival after nephrectomy and immunotherapy in patients with metastatic renal cell carcinoma: a stratification tool for prospective clinical trials. *Cancer* 2003; 98 (12): 2566-2575. Epub 2003/12/12. doi: 10.1002/cncr.11851
52. Rosenberg SA, Yang JC, White DE, Steinberg SM. Durability of complete responses in patients with metastatic cancer treated with high-dose interleukin-2: identification of the antigens mediating response. *Annals of Surgery* 1998; 228 (3): 307-319. Epub 1998/09/22.
53. Coppin C, Porzolt F, Kumpf J, Coldman A, Wilt T. Immunotherapy for advanced renal cell cancer. *Cochrane Database of Systematic Reviews* 2000; (3): CD001425. Epub 2000/07/25. doi: 10.1002/14651858.cd001425
54. Hammers HJ, Plimack ER, Infante JR, Rini BI, McDermott DF et al. Safety and efficacy of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma: the CheckMate 016 study. *Journal of Clinical Oncology* 2017; 35 (34): 3851-3858. Epub 2017/07/06. doi: 10.1200/JCO.2016.72.1985
55. Peccatori J, Barkholt L, Demirer T, Sormani MP, Bruzzi P et al. Prognostic factors for survival in patients with advanced renal cell carcinoma undergoing nonmyeloablative allogeneic stem cell transplantation. *Cancer* 2005; 104 (10): 2099-2103. doi: 10.1002/cncr.21477
56. Barkholt L, Bregni M, Remberger M, Blaise D, Peccatori J et al. Allogeneic haematopoietic stem cell transplantation for metastatic renal carcinoma in Europe. *Annals of Oncology* 2006; 17 (7): 1134-1140. doi: 10.1093/annonc/mdl086
57. Bregni M, Ueno NT, Childs R. The second international meeting on allogeneic transplantation in solid tumors. *Bone Marrow Transplantation* 2006; 38 (8): 527-537. Epub 2006/09/06. doi: 10.1038/sj.bmt.1705479
58. Tournigand C, Andre T, Achille E, Lledo G, Flesh M et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *Journal of Clinical Oncology* 2004; 22 (2): 229-237. Epub 2003/12/06. doi: 10.1200/jco.2004.05.113
59. Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *New England Journal of Medicine* 2004; 351 (4): 337-345. Epub 2004/07/23. doi: 10.1056/NEJMoa033025
60. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *New England Journal of Medicine* 2004; 350 (23): 2335-2342. Epub 2004/06/04. doi: 10.1056/NEJMoa032691
61. Sykes M, Preffer F, McAfee S, Saidman SL, Weymouth D et al. Mixed lymphohaemopoietic chimerism and graft-versus-lymphoma effects after non-myeloablative therapy and HLA-mismatched bone-marrow transplantation. *The Lancet* 1999; 353 (9166): 1755-1759. Epub 1999/05/29. doi: 10.1016/s0140-6736(98)11135-2
62. Hentschke P, Barkholt L, Uzunel M, Mattsson J, Wersall P et al. Low-intensity conditioning and hematopoietic stem cell transplantation in patients with renal and colon carcinoma. *Bone Marrow Transplantation* 2003; 31 (4): 253-261. Epub 2003/03/07. doi: 10.1038/sj.bmt.1703811
63. International germ cell consensus classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. *Journal of Clinical Oncology* 1997; 15(2): 594-603.
64. Aglietta M, Barkholt L, Schianca FC, Caravelli D, Omazic B et al. Reduced-intensity allogeneic hematopoietic stem cell transplantation in metastatic colorectal cancer as a novel adoptive cell therapy approach. The European group for blood and marrow transplantation experience. *Biology of Blood and Marrow Transplantation* 2009; 15 (3): 326-335. doi: 10.1016/j.bbmt.2008.11.036
65. Bay JO, Fleury J, Choufi B, Tournilhac O, Vincent C et al. Allogeneic hematopoietic stem cell transplantation in ovarian carcinoma: results of five patients. *Bone Marrow Transplantation* 2002; 30 (2): 95-102. Epub 2002/07/20. doi: 10.1038/sj.bmt.1703609
66. Bregni M, Peccatori J, Bernardi M, Pedrazzoli P, Siena S et al. Allogeneic stem cell transplantation in ovarian cancer: the EBMT experience. *Bone Marrow Transplantation* 2003; 31 (Suppl: 1, Oral abstract: 0275): S36. doi: doi.org/10.1038/sj.bmt.1703973
67. Bay JO, Cabrespine-Faugeras A, Tabrizi R, Blaise D, Viens P et al. Allogeneic hematopoietic stem cell transplantation in ovarian cancer-the EBMT experience. *International Journal of Cancer* 2010; 127 (6): 1446-1452. Epub 2010/01/06. doi: 10.1002/ijc.25149
68. Morecki S, Yacovlev E, Gelfand Y, Uzi I, Slavin S. Cell therapy with preimmunized effector cells mismatched for minor histocompatible antigens in the treatment of a murine mammary carcinoma. *Journal of Immunotherapy* 2001; 24 (2): 114-121.

69. Panigrahi S, Yacovlev E, Gelfand Y, Schuger L, Slavin S et al. Intraportal and systemic allogeneic cell therapy in a murine model of hepatic metastatic breast cancer. *Cytokines, Cellular & Molecular Therapy* 2002; 7 (3): 99-106. doi: 10.1080/13684730310001661
70. Carnevale-Schianca F, Ricchiardi A, Capaldi A, Bucci AR, Grignani G et al. Allogeneic hemopoietic stem cell transplantation in solid tumors. *Transplantation Proceedings* 2005; 37 (6): 2664-2666. Epub 2005/09/27. doi: 10.1016/j.transproceed.2005.06.050
71. Morecki S, Yacovlev E, Diab A, Slavin S. Allogeneic cell therapy for a murine mammary carcinoma. *Cancer Research* 1998; 58 (17): 3891-3895. Epub 1998/09/10
72. Kumar S, Ishii A, Yang HK, Venzon DJ, Kim SJ et al. Modulation of graft-versus-tumor effects in a murine allogeneic bone marrow transplantation model by tumor-derived transforming growth factor-beta1. *Biology of Blood and Marrow Transplantation* 2001; 7 (1): 25-30. Epub 2001/02/24. doi: 10.1053/bbmt.2001.v7.pm11215695
73. Deichman GI, Kashkina LM, Kluchareva TE, Vendrov EL, Matveeva VA. Inhibition of experimental and spontaneous lung metastases of highly metastatic Syrian hamster sarcoma cells by non-activated bone marrow and peritoneal exudate cells. *International Journal of Cancer* 1983; 31 (5): 609-615. Epub 1983/05/15.
74. Misawa A, Hosoi H, Tsuchiya K, Iehara T, Sawada T et al. Regression of refractory rhabdomyosarcoma after allogeneic stem-cell transplantation. *Pediatric Hematology and Oncology* 2003; 20 (2): 151-155. Epub 2003/01/30. doi: 10.1080/0880010390158658
75. Pedrazzoli P, Da Prada GA, Giorgiani G, Schiavo R, Zambelli A et al. Allogeneic blood stem cell transplantation after a reduced-intensity, preparative regimen: a pilot study in patients with refractory malignancies. *Cancer* 2002; 94 (9): 2409-2415. Epub 2002/05/17. doi: 10.1002/cncr.10491
76. Castagna L, Sarina B, Todisco E, Bramanti S, Bertuzzi A et al. Lack of activity of allogeneic stem cell transplantation with reduced-intensity conditioning regimens in advanced sarcomas. *Bone Marrow Transplantation* 2005; 35 (4): 421-422. Epub 2005/01/11. doi: 10.1038/sj.bmt.1704774
77. Secondino S, Carrabba MG, Pedrazzoli P, Castagna L, Spina F et al. Reduced intensity stem cell transplantation for advanced soft tissue sarcomas in adults: a retrospective analysis of the European Group for Blood and Marrow Transplantation. *Haematologica* 2007; 92 (3): 418-420. doi: 10.3324/haematol.10521
78. Alexander P, Delorme EJ, Hall JG. The effect of lymphoid cells from the lymph of specifically immunised sheep on the growth of primary sarcomata in rats. *The Lancet* 1966; 287 (7448): 1186-1189.
79. Ellman L, Katz DH, Green I, Paul WE, Benacerraf B. Mechanisms involved in the antileukemic effect of immunocompetent allogeneic lymphoid cell transfer. *Cancer Research* 1972; 32 (1): 141-148. Epub 1972/01/01.
80. Katz DH, Ellman L, Paul WE, Green I, Benacerraf B. Resistance of guinea pigs to leukemia following transfer of immunocompetent allogeneic lymphoid cells. *Cancer Research* 1972; 32 (1): 133-140. Epub 1972/01/01.
81. Symons HJ, Levy MY, Wang J, Zhou X, Zhou G et al. The allogeneic effect revisited: exogenous help for endogenous, tumor-specific T cells. *Biology of Blood and Marrow Transplantation* 2008; 14 (5): 499-509. Epub 2008/04/16. doi: 10.1016/j.bbmt.2008.02.013
82. Mapara MY, Kim YM, Wang SP, Bronson R, Sachs DH et al. Donor lymphocyte infusions mediate superior graft-versus-leukemia effects in mixed compared to fully allogeneic chimeras: a critical role for host antigen-presenting cells. *Blood* 2002; 100 (5): 1903-1909. Epub 2002/08/15. doi: 10.1182/blood-2002-01-0023
83. Falkenburg JH, Warren EH. Graft versus leukemia reactivity after allogeneic stem cell transplantation. *Biology of Blood and Marrow Transplantation* 2011; 17 (1 Suppl): S33-38. Epub 2011/01/14. doi: 10.1016/j.bbmt.2010.11.009
84. Harano M, Eto M, Iwai T, Tatsugami K, Kiyoshima K et al. Renal cancer treatment with low levels of mixed chimerism induced by nonmyeloablative regimen using cyclophosphamide in mice. *Cancer Research* 2005; 65 (21): 10032-10040. Epub 2005/11/04. doi: 10.1158/0008-5472.CAN-05-0457
85. Rubio MT, Saito TI, Kattleman K, Zhao G, Buchli J et al. Mechanisms of the antitumor responses and host-versus-graft reactions induced by recipient leukocyte infusions in mixed chimeras prepared with nonmyeloablative conditioning: a critical role for recipient CD4+ T cells and recipient leukocyte infusion-derived IFN-gamma-producing CD8+ T cells. *Journal of Immunology* 2005; 175 (2): 665-676. doi: 10.4049/jimmunol.175.2.665
86. De Somer L, Sprangers B, Fevery S, Rutgeerts O, Lenaerts C et al. Recipient lymphocyte infusion in MHC-matched bone marrow chimeras induces a limited lymphohematopoietic host-versus-graft reactivity but a significant antileukemic effect mediated by CD8+ T cells and natural killer cells. *Haematologica* 2011; 96 (3): 424-431. doi: 10.3324/haematol.2010.035329
87. Willems L, Fevery S, Sprangers B, Rutgeerts O, Lenaerts C et al. Recipient leukocyte infusion enhances the local and systemic graft-versus-neuroblastoma effect of allogeneic bone marrow transplantation in mice. *Cancer Immunology, Immunotherapy* 2013; 62 (11): 1733-1744. Epub 2013/10/02. doi: 10.1007/s00262-013-1479-6
88. Takeuchi A, Eto M, Tatsugami K, Yamada H, Yokomizo A et al. Renal cancer treatment with recipient lymphocyte infusion enhanced the antitumor effect of nonmyeloablative allogeneic stem cell transplantation. *Transplant Immunology* 2015; 32 (2): 131-139. Epub 2014/12/21. doi: 10.1016/j.trim.2014.12.001
89. Xu J, Tian K, Zhang H, Li L, Liu H et al. Chimeric antigen receptor-T cell therapy for solid tumors require new clinical regimens. *Expert Review of Anticancer Therapy* 2017; 17 (12): 1099-1106. Epub 2017/10/20. doi: 10.1080/14737140.2017.1395285

90. Yong CSM, Dardalhon V, Devaud C, Taylor N, Darcy PK et al. CAR T-cell therapy of solid tumors. *Immunology and Cell Biology* 2017; 95 (4): 356-363. Epub 2016/12/23. doi: 10.1038/icb.2016.128
91. Comoli P, Chabannon C, Koehl U, Lanza F, Urbano-Ispizua A et al. Development of adaptive immune effector therapies in solid tumors. *Annals of Oncology* 2019. doi: 10.1093/annonc/mdz285
92. Louis CU, Savoldo B, Dotti G, Pule M, Yvon E et al. Antitumor activity and long-term fate of chimeric antigen receptor-positive T cells in patients with neuroblastoma. *Blood* 2011; 118 (23): 6050-6056. doi: 10.1182/blood-2011-05-354449
93. Ahmed N, Brawley V, Hegde M, Bielamowicz K, Kalra M et al. HER2-Specific Chimeric Antigen Receptor-Modified Virus-Specific T Cells for Progressive Glioblastoma: A Phase I Dose-Escalation Trial. *JAMA Oncology* 2017; 3 (8): 1094-1101. doi: 10.1001/jamaoncol.2017.0184
94. O'Rourke DM, Nasrallah MP, Desai A, Melenhorst JJ, Mansfield K et al. A single dose of peripherally infused EGFRvIII-directed CAR T cells mediates antigen loss and induces adaptive resistance in patients with recurrent glioblastoma. *Science Translational Medicine* 2017; 9 (399). doi: 10.1126/scitranslmed.aaa0984
95. Brown CE, Alizadeh D, Starr R, Weng L, Wagner JR et al. Regression of Glioblastoma after Chimeric Antigen Receptor T-Cell Therapy. *New England Journal of Medicine* 2016; 375 (26): 2561-2569. doi: 10.1056/NEJMoa1610497
96. Beatty GL, Haas AR, Maus MV, Torigian DA, Soulen MC et al. Mesothelin-specific chimeric antigen receptor mRNA-engineered T cells induce anti-tumor activity in solid malignancies. *Cancer Immunology Research* 2014; 2 (2): 112-120. doi: 10.1158/2326-6066.CIR-13-0170
97. Feng KC, Guo YL, Liu Y, Dai HR, Wang Y et al. Cocktail treatment with EGFR-specific and CD133-specific chimeric antigen receptor-modified T cells in a patient with advanced cholangiocarcinoma. *Journal of Hematology & Oncology* 2017; 10 (1):4. doi: 10.1186/s13045-016-0378-7
98. Feng K, Guo Y, Dai H, Wang Y, Li X et al. Chimeric antigen receptor-modified T cells for the immunotherapy of patients with EGFR-expressing advanced relapsed/refractory non-small cell lung cancer. *Science China Life Sciences* 2016; 59 (5): 468-479. doi: 10.1007/s11427-016-5023-8
99. Zhang C, Wang Z, Yang Z, Wang M, Li S et al. Phase I Escalating-Dose Trial of CAR-T Therapy Targeting CEA(+) Metastatic Colorectal Cancers. *Molecular Therapy* 2017; 25 (5): 1248-1258. doi: 10.1016/j.ymthe.2017.03.010
100. Muul LM, Spiess PJ, Director EP, Rosenberg SA. Identification of specific cytolytic immune responses against autologous tumor in humans bearing malignant melanoma. *Journal of Immunology* 1987; 138 (3): 989-995.
101. Rosenberg SA, Restifo NP. Adoptive cell transfer as personalized immunotherapy for human cancer. *Science* 2015; 348 (6230): 62-68. doi: 10.1126/science.aaa4967
102. Besser MJ, Shapira-Frommer R, Treves AJ, Zippel D, Itzhaki O et al. Clinical responses in a phase II study using adoptive transfer of short-term cultured tumor infiltration lymphocytes in metastatic melanoma patients. *Clinical Cancer Research* 2010; 16 (9): 2646-2655. doi: 10.1158/1078-0432.CCR-10-0041
103. Saint-Jean M, Knol AC, Volteau C, Quereux G, Peuvrel L et al. Adoptive cell therapy with tumor-infiltrating lymphocytes in advanced melanoma patients. *Journal of Immunology Research* 2018; 2018: 3530148. doi: 10.1155/2018/3530148
104. Borch T, Andersen R, Ellebaek E, Met Ö, Donia M et al. Treatment with tumor-infiltrating lymphocytes in the changing treatment landscape of metastatic melanoma. *Journal of Clinical Oncology* 2019; 37 (15_suppl): e14024-e14024. doi: 10.1200/JCO.2019.37.15_suppl.e14024
105. Tran E, Turcotte S, Gros A, Robbins PF, Lu YC et al. Cancer immunotherapy based on mutation-specific CD4+ T cells in a patient with epithelial cancer. *Science* 2014; 344 (6184): 641-645. doi: 10.1126/science.1251102
106. Stevanovic S, Draper LM, Langhan MM, Campbell TE, Kwong ML et al. Complete regression of metastatic cervical cancer after treatment with human papillomavirus-targeted tumor-infiltrating T cells. *Journal of Clinical Oncology* 2015; 33 (14): 1543-1550. doi: 10.1200/JCO.2014.58.9093
107. Lindenberg MA, Retel VP, Van den Berg JH, Geukes Foppen MH, Haanen JB et al. Treatment with tumor-infiltrating lymphocytes in advanced melanoma: evaluation of early clinical implementation of an advanced therapy medicinal Product. *Journal of Immunotherapy* 2018; 41 (9): 413-425. doi: 10.1097/CJI.0000000000000245
108. Xu H, Yu S, Liu Q, Yuan X, Mani S et al. Recent advances of highly selective CDK4/6 inhibitors in breast cancer. *Journal of Hematology & Oncology* 2017; 10 (1): 97. Epub 2017/04/26. doi: 10.1186/s13045-017-0467-2
109. Demirer T, Ilhan O, Arat M, Genc Y, Ozcan M et al. CD41+ and CD42+ hematopoietic progenitor cells may predict platelet engraftment after allogeneic peripheral blood stem cell transplantation. *Journal of Clinical Apheresis* 2001; 16 (2): 67-73. doi: 10.1002/jca.1015
110. Demirer T, Ilhan O, Ayli M, Arat M, Dagli M et al. Monitoring of peripheral blood CD34+ cell counts on the first day of apheresis is highly predictive for efficient CD34+ cell yield. *Therapeutic Apheresis* 2002; 6 (5): 384-389. doi: 10.1046/j.1526-0968.2002.00406.x
111. Bakanay SM, Demirer T. Novel agents and approaches for stem cell mobilization in normal donors and patients. *Bone Marrow Transplantation* 2012; 47 (9): 1154-1163. doi: 10.1038/bmt.2011.170
112. Sahin U, Toprak SK, Atilla PA, Atilla E, Demirer T. An overview of infectious complications after allogeneic hematopoietic stem cell transplantation. *Journal of Infection and Chemotherapy* 2016. doi: 10.1016/j.jiac.2016.05.006
113. Kurt Yuksel M, Demirer T. Toxicity of Conditioning Regimens in Haploidentical SCT. In: Demirer T, editor. *Haploidentical Stem Cell Transplantation: An Emerging Treatment Modality*: Humana Press, Cham; 2017. pp. 43-56.
114. Demirer T. Preface. In: Demirer T, editor. *Haploidentical Stem Cell Transplantation: An Emerging Treatment Modality*: Humana Press, Cham; 2017.