AGvHD in Fanconi anemia and acquired aplastic anemia

ACUTE GRAFT-VERSUS-HOST DISEASE IN PATIENTS WITH FANCONI ANEMIA OR ACQUIRED APLASTIC ANEMIA UNDERGOING BONE MARROW TRANSPLANTATION FROM HLA IDENTICAL SIBLING DONORS: RISK FACTORS AND INFLUENCE ON OUTCOME.

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SUMMARY

To assess whether FA patients might be at risk for acute graft-versus-host disease (AGvHD) despite using low-intensity conditionings, we retrospectively analyzed the incidence of AGvHD and its impact on outcome in 37 FA patients and 73 patients with acquired aplastic anemia transplanted at Saint Louis Hospital from HLA-genotypic identical siblings with similar conditionings (thoraco-abdominal irradiation plus cyclophosphamide 20 [FA] or 150 mg/kg [AAA]). Despite being younger, FA patients had an increased risk of grade II-IV AGvHD (RR, 2.00, p=.021), especially in younger patients (RR, 7.93, p=.014). The risks of requiring systemic corticosteroids to treat AGvHD and experiencing cortico-resistant AGvHD were significantly increased in FA patients. Although non-FA and FA patients had similar 10-year outcomes, acute and chronic GvHD had a biphasic effect on FA patient outcome with an additional cluster of lethal events starting by 5 years post-transplant. This late survival fall, restricted to FA patients, was closely related to head-and-neck carcinomas (15-year incidence: 53%). FA patients represent a group at risk regarding AGvHD when using irradiation-based conditionings. The impact of AGvHD on survival may not be limited to the early post-transplant period, and may be a major risk factor for head-and-neck carcinomas and late mortality in FA patients.
INTRODUCTION

Fanconi anemia (FA) is an autosomal recessive disorder belonging to the group of chromosomal instability syndromes. The natural history of FA is to evolve toward progressive bone marrow failure, which is most often lethal before the end of the second decade of life without treatment. Allogeneic stem cell transplantation (SCT) is currently the only way to restore normal hematopoiesis in these patients. The increased sensitivity of FA cells to alkylating agents and ionizing radiations have been the main explanations to the poor outcome of FA patients receiving conventional preparative regimens for allogeneic bone marrow transplantation. The combination of low-dose cyclophosphamide and thoraco-abdominal irradiation (TAI), as proposed by Gluckman et al, has resulted in a major reduction of early multi-organ failures and severe acute graft-versus-host disease (AGvHD), leading to a dramatic decrease of the early transplant-related morbidity and mortality in FA patients transplanted with HLA identical siblings. Because FA cells display defective DNA repair processes and an increased sensitivity to the pro-apoptotic effects of tumor necrosis factor-α, γ-interferon and reactive oxygen species, i.e., cytokines directly or indirectly involved in AGvHD pathogenesis, we were concerned that FA patients might still have a high propensity to develop severe AGvHD following our low-dose preparative regimen. Therefore, we compared the incidence and clinical severity of AGvHD in patients with either FA or acquired aplastic anemia (AAA) who underwent transplantation from HLA identical donors using a similar combination of cyclophosphamide and TAI as preparative regimen, but at higher doses for AAA. In addition, we focused on the impact of AGvHD in these two groups of patients with respect to chronic GvHD, secondary malignancies, and overall survival.

METHODS

Patients

Included in the study were 110 patients with a primary diagnosis of AAA (n=73, non-FA group) or FA (n=37) who underwent bone marrow transplantation from HLA genotypic identical sibling donors at Saint Louis Hospital between January 1981 and December 1996. Fanconi anemia and AAA were defined according to standard criteria. The preparative regimens were cyclophosphamide 20 mg/kg total dose plus 5 Gy thoraco-abdominal irradiation (TAI) for FA patients, and cyclophosphamide 150 mg/kg total dose plus 6 Gy TAI for non-FA patients. Thoraco-abdominal irradiation was delivered with a linear accelerator as a single fraction with a dose rate of 12.9 cGy per minute. Both
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lungs, part of the right liver lobe, and testicles in males, were shielded. Cyclosporine (CsA) was used alone in FA patients for GvHD prophylaxis, and was started the day before graft infusion at a daily dose of 3 mg/kg given as a continuous infusion over 24 hours. Cyclosporine was given either alone (n=47) or combined with short-course methotrexate (MTX) (n=26) in non-FA patients, as previously described.14. Rules to manage CsA after graft infusion were the same in all patients, and were based on pharmacokinetics data, urea and creatinine levels. All patients were isolated in laminar air flow rooms for at least 30 days after graft infusion, and received oral broad-spectrum antibiotics and anti-fungal drugs to achieve total gut decontamination. Acyclovir was given for prevention of herpes simplex infections. Patients who had evolved to myelodysplastic syndrome or acute leukemia before transplantation, who received other conditioning regimens, GvHD prophylaxes, cord blood transplantation, G-CSF mobilized peripheral blood progenitor cells, or who did not achieve neutrophil recovery were excluded from this analysis. Main characteristics of the patients according to the underlying disease, and GvHD prophylaxis are summarized in Table 1.

Definitions and statistical analysis

Endpoints were assessed on the date of last patient contact and were analyzed on April 1, 2002. Acute and chronic GvHD were graded according to standard criteria.15-17. Acute GvHD was considered as cortico-resistant when methyl-prednisolone used at a daily dose of 2 mg/kg was unable to control AGvHD evolution. Therefore, patients who required anti T-cell monoclonal antibodies, anti-thymocyte globulins, methyl-prednisolone at a daily dose greater than 2 mg/kg, or any other immunosuppressive drug were considered as having cortico-resistant AGvHD. Analysis of chronic GvHD included patients who survived longer than 90 days from transplantation. Probabilities of grade I-IV, grade II-IV, grade III-IV, and cortico-resistant AGvHD, as well as the probability to receive systemic corticosteroid first line treatment for AGvHD by day+100 were computed from the time of transplantation using cumulative incidences and considering all death not related to AGvHD as the competing risk factor.18 Cumulative incidences were used to estimate the incidence of secondary malignancies, all causes of death not related to secondary malignancy being considered as the competing risk factor. The Gray test was used to compare cumulative incidences between groups.18 Estimate of the overall survival was computed according to the Kaplan-Meier product limit method.19 Groups were compared using the two-tailed log-rank test. P-spline
method and penalized Cox model were used to define the most appropriate cut-off value(s) for continuous covariates. The following covariates were analyzed in univariate analysis: primary diagnosis (non-FA vs. FA), etiology of the AAA (idiopathic vs. post-hepatitis vs. toxic or drug related), year of transplantation (continuous covariate), recipient age at transplantation (continuous covariate, and < 12 years vs. ≥ 12 years), recipient gender, use of androgens and/or anti-thymocyte globulins between diagnosis and transplantation, number of transfusion before transplantation (< 20 vs. ≥ 20, data available for FA patients only) nucleated cell dose infused (continuous covariate, and < 3x10⁹/kg vs. ≥ 3x10⁹/kg), donor gender, recipient/donor sex match, recipient/donor ABO blood group compatibility (no vs. minor or major incompatibility, major incompatibility vs. others), recipient cytomegalovirus serostatus before transplantation, and GvHD prophylaxis (CsA alone vs. CsA + MTX). For multivariate analysis, covariates found significant at P < .10 in univariate analysis were introduced in the Cox proportional hazards model and were selected through a stepwise procedure. Potential interactions between the significant covariates were tested adding cross-product terms to the model. Departure from the proportional hazards assumption was assessed using methods based on partial residuals and a graphical approach. If the proportional hazards assumption did not hold for a covariate, the extended Cox model with time-dependent covariate was used. When groups were compared according to continuous covariates, Mann Whitney U test or Kruskal-Wallis one-way ANOVA on ranks test were used for difference in medians. According to the group sizes, Chi-square analysis or Fisher exact test was used to compare categorical covariates. S Plus 2000 Professional 3 (Insightful, Seattle) was used for all statistical analysis.

RESULTS

Acute GvHD incidence, risk factors and organ involvement

Cumulative incidence of grade II-IV AGvHD in patients with AAA given CsA, CsA plus MTX, and in FA patients was 45% (95% confidence interval (CI), 29-57%), 42% (95%CI, 29-57%), and 62% (95%CI, 43-75%), respectively (p=.035). Fanconi anemia as primary diagnosis was the only significant predictor of grade II-IV AGvHD in univariate analysis (RR, 2.00, 95%CI, 1.17-3.43, p=.021). As for grade I-IV AGvHD (data not shown), the increased risk of grade II-IV AGvHD between FA and non-FA patients was mainly observed in recipients less than 12 years of age at the time of transplantation (Figure 1A). The difference between young FA and non-FA patients remained significant when
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GvHD prophylaxis was taken into consideration since grade II-IV AGvHD incidence was respectively 9% and 25% in young non-FA patients given CsA alone and CsA plus MTX, versus 72% in FA patients (p=.0013). In multivariate analysis, FA as primary diagnosis was significantly associated with grade II-IV AGvHD in FA patients less than 12 years of age at the time of transplantation (RR, 7.93, 95%CI: 1.52-41.43, p=.014), whereas younger age at transplantation had a protective effect for the non-FA patients (RR, 0.20, 95%CI, 0.05-0.84, p=.028). Fanconi anemia patients were not a population at risk with respect to grade III-IV AGvHD in univariate or multivariate analyses (RR, 1.13, 95%CI, 0.49-2.62). Regarding organ involvement, stages 2 to 4 were more frequently observed in FA than in non-FA patients (Skin: 46% vs. 36%, Gut: 19% vs. 16%, Liver: 22% vs. 16%), but the difference between these two groups only reached significance for stages 3 to 4 liver involvement (14% in FA vs. 1% in non-FA patients, p=.028).

**Acute GvHD treatments and response to first line therapy**

Fanconi anemia patients were more likely to receive corticosteroids as first line treatment for AGvHD than non-FA patients (Figure 1B). Focusing on patients less than 12 years of age at the time of transplantation, the probability to receive corticosteroids by day+100 post-transplant was 89% in FA patients (95%CI, 59-97%) versus 55% in non-FA patients given CsA alone (95%CI, 13-76%) and 75% in non-FA patients given CsA plus MTX (95%CI, 0-95%) (p=.039 when all three groups compared – probability, 60% for all non-FA patients, p=.011 when FA patients compared to all non-FA patients). In addition, FA patients more frequently required second line treatments, i.e., antithymocyte globulins (cumulative incidences: 27% vs. 10%, p=.015) and methyl-prednisolone daily doses greater than 2 mg/kg (cumulative incidences: 39% vs. 24%, p=.11), to control AGvHD. Focusing on the younger group of patients, FA was associated with an increased risk of experiencing cortico-resistant AGvHD (RR, 6.06, 95%CI: 1.32-27.8, Figure 1C), even if the type of GvHD prophylaxis used in the non-FA group was considered (data not shown).

**Predictors of acute GvHD in Fanconi anemia patients**

In univariate analysis, uro-genital malformations (RR, 4.67, 95%CI, 1.46-14.9, p<.01), donor / recipient ABO blood group incompatibility (RR, 4.40, 95%CI, 1.47-13.1, p<.01), and donor / recipient sex mismatch (RR, 3.31, 95%CI, 1.47-7.47, p<.01) were predictors of grade II-IV AGvHD. The only covariate associated with an increased risk of grade III-
IV AGvHD in FA patients was a donor / recipient major ABO blood group incompatibility (RR, 10.5, 95%CI, 3.09-36.0, p<.001). In addition, uro-genital malformations (RR, 3.09, 95%CI, 0.86-11.10, p=.08), and donor / recipient major ABO blood group incompatibility (RR, 6.02, 95%CI, 1.66-21.80, p<.01) were associated with an increased risk of cortico-resistant AGvHD. In univariate analysis, year of transplantation, time interval between diagnosis and transplantation, number of pre-transplant transfusions, and the use of androgens before transplantation were not significant predictors of AGvHD, whatever the considered grade was. No multivariate analysis was performed because of the small size of the FA group.

**Chronic GvHD and secondary malignancies**

Sixty-one percent of the overall group of patients experienced chronic GvHD, which was limited in 23 cases and extensive in 39 cases (assessable patients, n=101), respectively. Fanconi anemia as primary diagnosis (Odds ratio (OR), 2.69, 95%CI, 1.04-6.94, p=.04) and male recipient were covariates significantly associated with an increased risk of chronic GvHD. However, FA patients were not a population at risk with respect to extensive chronic GvHD (p=.75). Secondary malignancies occurred in eight FA patients and three non-FA patients (head and neck carcinoma, n=7, breast cancer, n=1, osteosarcoma, n=1, post-hepatitis C liver carcinoma, n=1, squamous cell carcinoma of the skin, n=1 - sex ratio, 9 males / 2 females). In addition, one FA patient developed severe oral leukodysplasia. Head and neck carcinomas were exclusively observed in FA patients, and were diagnosed at a median of 8.3 years after transplantation (range, 5.3 – 13.9 years), leading to a cumulative incidence of head and neck carcinoma in FA patients of 20% (95%CI: 9-44%) and 53% (95%CI: 31-93%) by 10 and 15 years post-transplant, respectively. By 10 years post-transplantation, grade II-IV AGvHD (Figure 2) and chronic GvHD (cumulative incidence if occurred, 23%) were significant predictors of head and neck carcinomas, which were only observed in FA patients experiencing one of these two complications.

**Overall survival**

The 10-year post-transplant estimated survival of FA patients was similar to the one of non-FA patients whatever their GvHD prophylaxis was (Kaplan-Meier estimates: 57% in FA patients, 56% in AAA patients given CsA, 58% in patients given CsA plus MTX, p=NS). In addition, eight deaths occurred more than 10 years from transplantation.
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(patients at risk, n=43), which were related to secondary malignancies in six cases (FA patients, n=5). In multivariate analysis, a primary diagnosis of FA did not significantly affect the 10-year overall survival (RR, 0.89, 95%CI, 0.35-2.27, p=.80), and no interaction between FA and the other significant covariates (major ABO incompatibility, recipient age at transplantation, interval between diagnosis and transplantation) reached significance. These results were not modified with the introduction of post-transplant covariates such as grade II-IV, grade III-IV, or cortico-resistant AGvHD. However, the outcome of FA and non-FA patients along the first 10 years post-transplant was different. By 5 years post-transplant, FA patients who experienced grade II-IV AGvHD had an estimated survival of 69% (95%CI, 52-91%), which was slightly higher than the one of non-FA patients (Kaplan-Meier estimate: 44%, 95%CI, 30-66%, p=.11). However, by 10 years post-transplant, while the survival curve remained stable in the non-FA group, it has significantly fallen below 40% in the FA group, mainly because of secondary malignancies (Figure 3A). Considering cortico-resistant AGvHD, the impact of this complication was mainly observed during the first 18 months post-transplant in the non-FA group, whereas it was biphasic in the FA group, with a first impact during the first 18 months post-transplant - as for non-FA patients - and a second cluster of events observed after 5 years post-transplant, which was closely related to the occurrence of secondary malignancies (Figure 3B). Considering chronic GvHD, such a two-step process affecting survival could also be identified (Figure 3C).

DISCUSSION

In this retrospective monocentric study about allogeneic bone marrow transplantation using an irradiation-based preparative regimen and HLA identical siblings for aplastic anemia, we found that FA patients had an increased risk of experiencing AGvHD when compared to patients with AAA. Despite FA patients were conditioned using a reduced-intensity preparative regimen, a dramatic difference of grade II-IV AGvHD incidence was observed, especially when considering patients less than 12 years of age, which represent the majority of FA patients undergoing transplantation. Surprisingly, when considering the "older patients" group, no significant difference in term of AGvHD incidence was observed between FA and non-FA patients. Since these older FA patients had less pronounced FA phenotypes, such as less frequent extensive malformative syndromes (11% vs. 44%, p=.02) or renal malformations (22% vs. 72%, p=0.003) for instance, they might indeed represent a distinct group of FA patients with respect to the
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characteristics of their intrinsic disease, leading to a different post-transplant outcome. In that way, it has already been shown that mosaicism could be a risk factor for graft failure in the setting of unrelated donor transplantations in FA\textsuperscript{22}. Our previous study analyzing results from unrelated transplantations in FA showed that patients with uro-genital and/or renal malformations had an increased risk of severe AGvHD in this setting\textsuperscript{23}. In the present study, we also found that uro-genital malformations were associated with an increased risk of grade II-IV and cortico-resistant AGvHD. An Italian study has also found that uro-genital malformations were associated with an increased risk of grade II-IV AGvHD in FA patients receiving stem cell transplantation from HLA-matched related donors\textsuperscript{24}. Taken together, these findings support the hypothesis that the impaired DNA repair process and increased tendency of the cells to undergo apoptosis under stressing conditions might be important factors influencing the occurrence and severity of AGvHD in FA.

The high incidence of AGvHD requiring systemic corticosteroid therapy and the substantial number of FA patients for whom additional immunosuppressive therapies were needed (cumulative incidence of cortico-resistant AGvHD in FA patients, 43%), point out that a more intense GvHD prophylaxis should be proposed. There is no convincing evidence in children bone marrow transplantation, that combining MTX to CsA would result in a synergistic effect to prevent AGvHD\textsuperscript{25}. Here in this study, the addition of MTX to CsA was associated with a delayed onset of AGvHD rather than with a decreased incidence of that complication in non-FA patients. These findings suggest that the addition of MTX to CsA in FA patients is unlikely to decrease the overall incidence of AGvHD. Various approaches are currently available to decrease the incidence of AGvHD in FA patients. The use of antithymocyte globulins combined to low-dose corticosteroid during the preparative regimen phase and after graft infusion as an \textit{in-vivo} T-cell depletion method as been shown to dramatically reduce the incidence of AGvHD in a small set of FA patients transplanted from HLA-identical siblings after a similar preparative regimen\textsuperscript{26}. \textit{Ex-vivo} T-cell depletion is currently under investigation in this setting as well. However, these two attractive approaches deserve attention with respect to the potential risk of increasing the immune deficiency during the first months post-transplantation, leading to higher transplant-related morbidity and mortality due to opportunistic infections and graft rejections. Mycophenolate mofetil, which exerts a stronger synergistic effect than MTX when used with CsA to prevent AGvHD, could be
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the immunosuppressive drug of choice to combine with CsA in FA patients\textsuperscript{27,28}. Our preliminary results with this drug have not been associated with a delayed hematopoietic recovery, a potential side-effect that has been observed after prolonged use of this drug. Whether mycophenolate mofetil will be associated with an increased risk of opportunistic infections will require further investigations. Irradiation-free preparative regimens based on an intermediate-dose of cyclophosphamide alone have also given some encouraging results with a 13\% AGvHD incidence in a group of 16 FA patients\textsuperscript{29}. Recent results on a limited number of patients also suggest that fludarabine, which has a more restricted cytotoxicity, but a potent immunosuppressive effect, could advantageously replace TAI regarding early transplant-related complications in FA or AAA patients\textsuperscript{30-34}.

It has been shown that FA patients, in a non-transplanted setting, have an increased risk of developing head and neck carcinomas when compared to a control normal population\textsuperscript{35}. In this study, acute GvHD, maybe by triggering chronic GvHD, had a dramatic influence on the risk of developing such lethal malignancies in FA patients. Therefore, reducing AGvHD incidence by one of the approaches described above should improve not only the early post-transplant outcome but also the long-term outcome of FA patients. Whether the high incidence of post-transplant head and neck carcinomas reported in our FA patients is related to the use of an irradiation based preparative regimen cannot be solved in this study since we had no control group of FA patients transplanted in our institution with an irradiation-free preparative regimen during the same time period. However, irradiation-free preparative regimens, by avoiding an additional risk factor interacting with the main biological defect of FA, i.e., DNA repair processes, could be currently the optimal strategy to consider in FA patients undergoing HLA geno-identical transplantation in the absence of clonal evolution.

\textbf{REFERENCES}


Table 1. Descriptive statistics according to primary disease, and GvHD prophylaxis.

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<th>Diseases</th>
<th>AAA (^1) TAI (^2)</th>
<th>AAA TAI CsA (^3)</th>
<th>AAA TAI CsA + MTX (^4)</th>
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*\(a\), \(b\), \(c\) represent the lower quartile, the median, the upper quartile for continuous covariates.
N is the number of non-missing values. Numbers after percents are frequencies.
\(^1\) AAA: acquired aplastic anemia, \(^2\) TAI: thoraco-abdominal irradiation, \(^3\) CsA: cyclosporine.
\(^4\) MTX: methotrexate, \(^5\) ATG: anti-thymocyte globulins, \(^6\) at least 3 anatomic sites involved (Ref. 32).
\(^\#\) CMV: cytomegalovirus, \(^\S\) BMT: bone marrow transplantation.
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LEGENDS

Figure 1. Cumulative incidences of grade II-IV and cortico-resistant acute GvHD according to primary diagnosis and recipient age at the time of transplantation.
(1A) Cumulative incidence of grade II-IV AGvHD in patients less than 12 years of age at the time of transplantation was 72% in FA (___, n=18) vs. 13% in non-FA patients (_._., n=15) (p=.0012). Cumulative incidence of AGvHD for patients of at least 12 years of age at the time of transplantation was 53% in FA (- - - , n=19) vs. 52% in non-FA patients (_..._, n=58) (p=NS).

(1B) Probability of requiring systemic corticosteroid therapy for treatment of AGvHD by day+100 post-transplant was 85% in FA patients (___) vs. 70% in non-FA patients given CsA alone (___) and 81% in non-FA patients given CsA plus MTX (- - - ) (p=.045 when all three groups compared – probability, 74% for all non-FA patients, p=.013 when FA patients compared to all non-FA patients).

(1C) Cumulative incidence of cortico-resistant AGvHD in patients less than 12 years of age at the time of transplantation was 56% in FA (___, n=18) vs. 13% in non-FA patients (_._., n=15) (p=.008). Cumulative incidence of cortico-resistant AGvHD in patients of at least 12 years of age at the time of transplantation was 29% in FA (_..._, n=19) vs. 38% in non-FA patients (- - - , n=58) (p=NS).

Figure 2. Cumulative incidence of head and neck carcinomas in Fanconi anemia patients according to the occurrence of grade II-IV AGvHD.
The 10-year cumulative incidence of head and neck carcinomas in FA patients experiencing grade II-IV AGvHD was 28% (___) vs. 0% for those who did not develop this complication (_ _ _) (p<.001).

Figure 3. Post-transplant estimated survival according to primary diagnosis and occurrence of grade II-IV, cortico-resistant AGvHD or chronic GvHD.
(A) The 10-year estimated survival of FA patients experiencing grade II-IV AGvHD was 38% (___) vs. 41% for non-FA patients (_.__) (p=NS). The 10-year estimated survival of FA patients who did not experience grade II-IV AGvHD was 92% (- - - ) vs. 69% for non-FA patients (_..._, p=NS).

(B) The 10-year estimated survival of FA patients experiencing cortico-resistant AGvHD was 37% (___) vs. 27% for non-FA patients (_.__) (p=NS). The 10-year estimated
survival of FA patients who did not experience cortico-resistant AGvHD was 81% ( - - - ) vs. 73% for non-FA patients ( ..._..._ ) (p=NS).

(C) The 10-year estimated survival of patients experiencing chronic GvHD was 54% for FA patients ( ____ ) and 65% for non-FA patients ( ..._..._ ), respectively (p=NS). The 10-year estimated survival of FA patients who did not experience chronic GvHD was 86% ( - - - ) vs. 59% for non-FA patients ( .-.-. ) (p=NS).
AGvHD in Fanconi anemia and acquired aplastic anemia

Figure 1B
Figure 1C
Figure 2
AGvHD in Fanconi anemia and acquired aplastic anemia

Figure 3A
AGvHD in Fanconi anemia and acquired aplastic anemia

Figure 3B
AGvHD in Fanconi anemia and acquired aplastic anemia

Figure 3C
Acute graft-versus-host disease in patients with Fanconi anemia or acquired aplastic anemia undergoing bone marrow transplantation from HLA identical sibling donors: risk factors and influence on outcome

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