Administration of a Phorbol Ester to Patients with Hematological Malignancies: Preliminary Results from a Phase I Clinical Trial of 12-O-Tetradecanoylphorbol-13-acetate

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ABSTRACT


Experimental Design: TPA was administered to patients with relapsed/refractory hematological malignancies.

Results: Phenotypic effects were detected in malignant cells and TPA-associated biological activity was present in blood for up to several hours after the infusion.

Conclusions: These studies confirm the feasibility of TPA administration to humans and establish the foundation for the development of phorbol esters as therapy for patients with a variety of malignant and nonmalignant disorders.

INTRODUCTION

Crotum tiglium L is a shrub of the Euphorbiaceae family. The croton oil obtained from Crotum tiglium L contains TPA, an agent that has been studied widely as a differentiation agent, tumor promoter, and modulator of multiple cellular signaling pathways. Its role as a tumor promoter was established by studies demonstrating TPA-induced development of tumors on the skin of mice previously treated with polycyclic aromatic hydrocarbons (1–5). Topical application of TPA alone twice/week for several months resulted in only an occasional papilloma. The activity of TPA as a hematopoietic cell differentiating agent has been established by studies of HL60, U937, K562, and NB4 leukemia cell lines, primary human acute myeloid leukemia cells, and normal hematopoietic stem cells (6–9). In these cells, TPA induces phenotypic alterations in morphology, immunophenotype, and function that are characteristic of cellular maturation along distinct hematopoietic pathways. In addition to the induction of differentiation in these primary cells and cell lines, TPA has been demonstrated to modulate the growth, differentiation, survival, function, and metabolism of a variety of other primary cells and cell lines. The broad range of these phorbol ester-mediated biological effects suggests a role for these drugs in the modulation of a variety of cellular processes, including those that affect the development, progression, and therapy of human malignancies.

At the cellular level, many, but not all, TPA-induced effects are mediated by the temporal activation, translocation, and suppression of selected PKC isoforms (10–13). These isoenzymes play central roles in signaling pathways, participating in a variety of protein phosphorylation cascades that regulate/modulate cellular structure and gene expression (10–12, 14–20). The exact pattern of kinase activation varies among cell types because different isoforms of PKC (with different subcellular sites of localization and half-life) predominate in different cells. Furthermore, the biological effects of the activation of a given subset of PKC isoforms in any cell will be variable, dependent upon the status of several interwoven signaling and regulatory pathways controlled by a variety of extracellular and intracellular stimuli.

The targets of PKC are incompletely defined, but the phosphorylation cascades that are initiated result in a network of signaling that participates in the regulation of proliferation,
differential, mitogenesis, apoptosis, and cytoskeletal structure/function (10–12, 14–20). PKC and related/downstream signaling pathways (e.g., MAPKs) also play important roles in the generation, maintenance, or progression of many malignancies. For example, PKC is a necessary cooperating oncogenic factor for mutated ras in some systems (14–16, 20–26) and regulates bcl-2 in others (26–30). Furthermore, phosphatidylinositol 3’-kinase mediated growth promoting, and antiapoptotic effects are PKC-dependent in some cell types (15, 16, 20, 29, 30). Therefore, the specific cellular outcomes associated with TPA exposure in malignant cells are likely dependent upon intricate and cell type-specific relationships between PKC isoforms, PKC downstream kinase cascades, other interacting signaling pathways, baseline cellular physiology, and genotypic features of the cells.

TPA may also modulate cellular responsiveness to cytokines and other ligands. Hence, different effects may occur after in vivo and ex vivo exposure to TPA. Metabolic and biological parameters may also result in marked differences between in vivo and ex vivo exposure to TPA. In fact, before this study, it was unknown if the isolated administration of TPA to patients resulted in any measurable cellular effects.

The capacity of TPA to induce phenotypic changes characteristic of differentiation and/or apoptosis in cell lines and primary malignant cells led investigators in China to administer TPA to patients with myeloid malignancies (31). A variety of doses and schedules, often in conjunction with cytarabine or 1,25-dihydroxyvitamin D3, were used. Clinical efficacy was detected, and the most prominent adverse effects included fevers, chills, dyspnea, hematuria, and phlebitis. These adverse effects were transient and repeat cycles of treatment were administered to most patients. Other patients in China have received TPA to attenuate chemotherapy-induced leukopenia (32). The tolerability of TPA (administered at a fixed dose in conjunction with cytarabine or 1,25-dihydroxyvitamin D3) in China prompted the initiation of a Phase I clinical trial of TPA as a single agent for patients with myeloid malignancies in China; and (c) the availability of leukemic cells in blood for analysis of TPA-induced effects in vivo. Recently, the clinical trial was expanded to include patients with any relapsed/refractory malignancy for which there are no standard antineoplastic options likely to result in disease response and/or symptom palliation.

Treatment. TPA was initiated at a dose of 0.063 mg/m² administered i.v. over 1 h on days 1 and 8. Repeat cycles were allowed after a 2-week rest if the patient was clinically stable and all toxicities had reversed. Dose escalation in increments of 0.063 mg/m² was undertaken if 3 consecutive patients did not experience dose-limiting toxicity (irreversible grade 2 or any grade 3–4 nonhematological toxicity). An additional 3 patients were treated at the same dose if any patient had dose-limiting toxicity. If 2 patients developed dose-limiting toxicity at any dose level, the preceding test dose would be labeled the maximally tolerated dose. After enrollment of the 11th patient, the protocol was amended in concert with the Food and Drug Administration to allow analysis of biological and clinical effects after acute and chronic administration of TPA. In the amended protocol, TPA was administered as an hourly infusion on days 1 and 8 followed by a 2-week rest period. TPA was then administered on 5 consecutive days for 2 consecutive weeks. The starting dose level reverted to 0.063 mg/m²/dose when the protocol was amended.

Biological Assay for TPA. In the absence of a physical assay for TPA, a biological assay for HL60 differentiating activity in blood was developed. Details of the method will be reported separately. The method involves two extractions of a 1-ml blood sample with 5 ml of ethyl acetate, evaporation of the ethyl acetate, redissolving the extraction residue in 50 µl of ethanol, and addition of an aliquot to HL60 cells. Adherent cell number is measured 48 h later and taken as an index of differentiation. Multiple positive control blood samples (obtained before administration of TPA) with known amounts of added TPA are assayed side-by-side with the experimental samples.

Immunophenotypic Analysis of Cells. Mononuclear cells obtained by ficoll-hypaque separation of blood at various
images were analyzed with the Pathways software. A phosphorimage screen for the appropriate time and scanned on a Molecular Dynamics Storm PhosphorImager. The scanned labeling reaction. The probes were hybridized to the cDNA (Inc.). Approximately 5 μg of RNA samples were used in each labeling reaction. The probes were hybridized to the cDNA array filters at 46°C. The washed probes were then exposed on a phosphorimage screen for the appropriate time and scanned on a Molecular Dynamics Storm PhosphorImager. The scanned images were analyzed with the Pathways software.

RESULTS

Administration of TPA to Patients. As of July 2001, 14 patients with hematological malignancies have been treated with TPA in our Phase I trial. Patient characteristics are presented in Table 1. Initial patients were treated with a single infusion of TPA on days 1 and 8 followed by a 2-week rest period. Repeat cycles were administered to patients who did not have overt disease progression. Currently, patients are treated on days 1 and 8 followed by a 2-week rest period after which daily infusions for 5 consecutive days on 2 consecutive weeks are administered. This dosing schedule was introduced to allow analysis of TPA-induced biological effects after both short- and longer-term administration (e.g., after the first dose of therapy and after treatment for 5 consecutive days on 2 consecutive weeks). Repeat cycles are allowed based upon clinical status. The majority of patients have had relapsed/refractory ANLL.

The Phase I trial was initiated using low doses of TPA (0.063 mg/m²). One patient with ANLL had stable disease (relapsed/refractory ANLL) for >3 months and received eight infusions. Transient declines in the number of circulating leukemia cells, as well as alterations of leukemic cell immunophenotype, have been seen in some patients in association with TPA treatment. However, none of these effects have been durable. There has been no correlation of toxicity or other biological effect with pharmacokinetic data. None of the patients with ANLL treated to date have had a remission. A patient with ANLL-M2 had a partial response.

Table 1. Patient information

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>TPA dose (mg/m²)</th>
<th>Doses</th>
<th>Diagnosis</th>
<th>Cytogenetics</th>
</tr>
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<tbody>
<tr>
<td>001</td>
<td>73</td>
<td>F</td>
<td>0.063</td>
<td>4</td>
<td>ANLL-M2</td>
<td>Normal</td>
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<tr>
<td>002</td>
<td>73</td>
<td>M</td>
<td>0.063</td>
<td>2</td>
<td>2° ANLL-M5</td>
<td>+8, -16</td>
</tr>
<tr>
<td>003</td>
<td>60</td>
<td>M</td>
<td>0.063</td>
<td>2</td>
<td>ANLL-M5</td>
<td>+13</td>
</tr>
<tr>
<td>004</td>
<td>72</td>
<td>F</td>
<td>0.125</td>
<td>2</td>
<td>2° ANLL-M5</td>
<td>1q−</td>
</tr>
<tr>
<td>005</td>
<td>63</td>
<td>F</td>
<td>0.125</td>
<td>1</td>
<td>ANLL-M5</td>
<td>Normal</td>
</tr>
<tr>
<td>006</td>
<td>74</td>
<td>M</td>
<td>0.125</td>
<td>3</td>
<td>MDS (RAEB-IT)</td>
<td>Normal</td>
</tr>
<tr>
<td>007</td>
<td>44</td>
<td>F</td>
<td>0.125</td>
<td>2</td>
<td>2° ANLL-M4</td>
<td>5q- 7q- 20q</td>
</tr>
<tr>
<td>008</td>
<td>68</td>
<td>F</td>
<td>0.125</td>
<td>8</td>
<td>ANLL-M5</td>
<td>Normal</td>
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<tr>
<td>009</td>
<td>64</td>
<td>F</td>
<td>0.125</td>
<td>2</td>
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<tr>
<td>010</td>
<td>76</td>
<td>M</td>
<td>0.125</td>
<td>2</td>
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<td>Normal</td>
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<td>011</td>
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<td>0.125</td>
<td>2</td>
<td>ANLL-M0</td>
<td>Complex</td>
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<tr>
<td>012</td>
<td>61</td>
<td>M</td>
<td>0.063</td>
<td>18</td>
<td>ANLL-M5</td>
<td>Complex</td>
</tr>
<tr>
<td>013</td>
<td>61</td>
<td>M</td>
<td>0.063</td>
<td>6</td>
<td>Chronic myelogenous leukemia-myeloid</td>
<td>9,22</td>
</tr>
<tr>
<td>014</td>
<td>29</td>
<td>F</td>
<td>0.063</td>
<td>21</td>
<td>Hodgkin’s disease</td>
<td>Not performed</td>
</tr>
</tbody>
</table>

a Fourteen patients treated with TPA on a Phase I clinical trial for patients with relapsed/refractory malignancies. The last 3 patients listed were treated with a modified dosing regimen that included treatment on days 1 and 8, followed by a 2-week rest period and daily therapy for 5 consecutive days on 2 consecutive weeks. Doses refer to the total number of doses of TPA administered.

b MDS (RAEB-IT), myelodysplasia (refractory anemia with excess blasts in transformation).
TPA allows pharmacokinetic studies that support the analysis of these patients required cystoscopy for evacuation of clots. Two patients developed macroscopic hematuria. One of these patients required cystoscopy for evacuation of clots. In one of those patients, a flare reaction at the initial site was detected immediately after TPA infusion in a contralateral arm vein 1 week later. Subsequent patients received the drug administered directly into a central infusion in a contralateral arm vein. Two patients developed phlebitis immediately after infusion via a peripheral vein. Two patients developed macroscopic hematuria. One of these patients required cystoscopy for evacuation of clots.

**Pharmacokinetics.** The development of an assay for TPA allows pharmacokinetic studies that support the analysis of in vivo effects of TPA. It was our objective to establish a mass spectrometry assay for TPA, however, it has been difficult to measure <2–4 ng/ml of TPA with current instrumentation.

In the absence of a physical assay for TPA, a biological assay for HL60 differentiating activity in blood was developed (“Materials and Methods”). Using this assay, we were able to detect HL60 differentiating activity in blood immediately after the TPA infusion in all patients, and in 8 of the patients, there was detectable activity at 3 h (2 h after completion of the infusion). The amount of TPA-like activity in blood ranged from 0.31 to 5.3 ng/ml immediately after the infusion and from undetectable to 3.6 ng/ml 2 h later. The mean TPA biological activity 2 h after infusion corresponded to 0.47 ± 0.26 ng/ml (SD) calculated from 13 infusions in 6 patients. The calculated terminal half-life was 11.1 ± 3.9 h (mean ± SD from five infusions in 4 patients). There was no correlation of TPA-like activity in blood with any clinical or immunophenotypic features (see below).

**Alteration in Patterns of Gene Expression During TPA Treatment.** Immunophenotypic analysis of leukemic blasts from 9 patients with ANLL was undertaken before and 24–48 h after administration of TPA. In these studies, alterations in antigen expression were considered significant if there were >20% changes in the number of gated leukemic cells that expressed the antigen or if there were significant changes in the intensity of antigen expression when analyzed in parallel to samples obtained before exposure to TPA. The leukemic cells from 2 of the patients could not be adequately analyzed because there were too few circulating leukemic blasts. Analysis of the leukemic cells from the remaining 7 patients revealed a TPA-associated increase in CD13 expression in 3 patients, whereas CD14 expression on leukemic cells was increased after TPA administration in 2 patients and decreased in 2 patients. CD7 expression was increased in 3 patients after administration of TPA. There was no correlation of immunophenotypic alterations with each other or with other clinical or cellular parameters, including blood levels of TPA biological activity (i.e., there was no correlation of immunophenotypic alterations with pharmacokinetic data).

With respect to gene expression, we evaluated the expression profiles of blood leukemic cells obtained from 2 patients before and after the administration of TPA. Both were elderly (>60 years old) with relapsed/refractory ANLL. In each patient, leukemia occurred in the setting of an antecedent hematological disorder, and the disease relapsed after induction followed by consolidation chemotherapy. One of the patients experienced a transient decline in blasts after treatment with TPA, the other patient had no apparent clinical response. Comparable levels of TPA-associated biological activity were detected in the blood of each patient 2 h after completion of the infusion. Ex vivo treatment with TPA induced morphological changes (change in cell shape with long projections and adherence to plastic) in the “responding” patient’s leukemia cell sample (Fig. 1) but not in the “nonresponder’s” leukemic cells. Complementary DNA arrays (Research Genetics filters; Refs. 33–35), containing ~4200 PCR products derived from amplification of expressed sequence tag inserts, were hybridized with radiolabeled cDNA prepared from each patient’s leukemic cell RNA obtained before and 24 h after TPA administration. Differential expression representations of scanned phosphorimages were made with Pathways software. Analysis of the hybridization patterns revealed that the sample from the nonresponding cells exhibited no alterations in gene expression after in vivo administration of TPA to the patient. In contrast, the cells from the patient whose cells responded to TPA treatment ex vivo (and had a transient decline in leukemic blasts in vivo) showed an altered pattern of gene expression after in vivo exposure to TPA. For example, significant (>3X) increases in the expression of a variety of genes was detected (Table 2). Of note, CREB and c-jun are induced by TPA in several cell lines as well. Other genes

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**Fig. 1** Morphological changes after ex vivo exposure of a patient’s ANLL cells to TPA. A, cells maintained in tissue culture for 24 h in the absence of TPA (40 ng/ml). B, cells maintained in tissue culture for 24 h in the presence of TPA (40 ng/ml).
induced after TPA administration included genes implicated in signal transduction, morphology/adhesion, cellular metabolism, chromatin remodeling, and differentiation (Table 2). These determinations demonstrate the capacity of TPA to modulate gene expression in leukemic cells in vivo. Thus, it is feasible to assess alterations in global patterns of in vivo gene expression after treatment with TPA. Some of the changes in gene expression appear to overlap with TPA-induced changes in HL60 cells (36–43).

**DISCUSSION**

Normal cellular growth, development, differentiation, and physiological function is dependent upon the integration of diverse environmental signals. Soluble and insoluble mediators interact with cellular receptors to initiate signaling pathways that modulate cellular function. Multiple pathways may be initiated by a given stimulus, and the phenotypic alterations induced by these pathways are a consequence of how they interact with each other in the context of the baseline physiological state of the cell.

With respect to human malignancy, the activity of these pathways is critically important to the development, maintenance, and progression of the disease. Signaling pathway alterations have been detected frequently in many human malignancies. For example, ras mediates signals from membrane receptors to cytoplasmic kinase cascades, including MAPK. Activated ras is bound to GTP and mediates the phosphorylation/activation of a spectrum of effector molecules, including upstream MAPK pathway kinases that activate extracellular signal-regulated kinase 1 and 2 and alter the activity of bcl-2 family members, phosphatidylinositol 3'-kinase pathway components, and a host of other molecules and pathways that drive proliferation, differentiation, and/or apoptosis. In normal cells, the activity of these ras-activated pathways often directs the cells toward a state of preparedness for cell proliferation. This preparedness includes energy mobilization, cell cycle progression, and suppression of apoptosis. In malignant cells, the constitutive activation of ras and selected other pathway components (e.g., receptor and nonreceptor tyrosine kinases, downstream signaling components, and so on) may partially mediate the oncogenic phenotype.

Exposure of human malignant cells to phorbol esters might impact on aberrant signaling pathways in a variety of ways. Acute exposure to phorbol esters can activate classic and novel PKC isoforms, and chronic exposure to phorbol esters can down-regulate the activity of these PKC isoforms (10–12, 14, 39). TPA reduces proliferation and induces monocytic/macrophage markers in HL60 cells, other cultured myelocytic leukemia cell lines, and primary leukemic cells (6–9, 35–38). Markers of differentiation in response to TPA include morphological appearance, decline in rate of replication, attachment to plastic (adherence), immunophenotypic changes (alterations in the expression of CD33, CD13, CD11b, CD14, CD7, CD9), new functional activities, and changes in histochemical staining. Hence, TPA-inducible effects may alter cellular phenotype in a variety of ways. Modulation of cellular proliferation, differentiation and/or apoptosis may occur, depending upon cell type, genetic alterations, and physiological state of the cell.

Despite ample evidence of phorbol ester-mediated biological effects in cell culture, the complexity of the interacting signaling pathways modulated by PKC makes it difficult to predict the biological outcome in any given malignant cell type. The diversity of PKC-mediated effects, the presence of non-PKC TPA receptors (13), the capacity of TPA to differentially modulate PKC isoforms in a temporal fashion (10–19, 44), and the lack of information concerning the durability of biological effects contribute to the complexity of predicting biological outcome after administration of phorbol esters to humans. In fact, the only data describing in vivo biological effects of phorbol ester administration to humans is available from the patients treated in China, and in those studies, most patients received combination therapies containing chemotherapeutic drugs and/or 1,25-dihydroxyvitamin D3 in addition to TPA (31).

A variety of compounds with the capacity to modulate PKC have been studied (11). These vary in selectivity, potency, and isoenzyme preference. One such agent, bryostatin 1, is being evaluated in clinical trials (45–52). Both TPA and bryostatin 1 result in activation followed by down-regulation of specific PKC isoforms. However, different, sometimes divergent, biological effects may be seen after exposure of cells to these two agents (14, 53–56). Differences in binding affinity to specific PKC isoforms and/or interactions with non-PKC targets may explain some of these differences. The capacity of TPA to induce differentiation of hematopoietic cell lines at low concentrations, the distinct pattern of induced biological effects, and the established effects of TPA on defined signaling pathways supports its development as a novel therapeutic agent, distinct from other PKC-modulating agents.

TPA administration in our study resulted in detectable biological effects in blood after a 1-h infusion. TPA-induced effects on gene expression and immunophenotype were seen, and some of these phenotypic alterations overlap with those induced in cell lines ex vivo. CD13 is a marker associated with myeloid differentiation, and levels of expression were increased

### Table 2

<table>
<thead>
<tr>
<th>Gene</th>
<th>Fold increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>MHC I</td>
<td>9.7</td>
</tr>
<tr>
<td>TGF-β</td>
<td>3.0</td>
</tr>
<tr>
<td>cGMP-dependent protein kinase β</td>
<td>4.3</td>
</tr>
<tr>
<td>Protein tyrosine kinase 7</td>
<td>3.1</td>
</tr>
<tr>
<td>Cytokine receptor family II, 4</td>
<td>3.4</td>
</tr>
<tr>
<td>NOTCH</td>
<td>5.3</td>
</tr>
<tr>
<td>Ubiquitin A-52</td>
<td>8.8</td>
</tr>
<tr>
<td>BAF60b</td>
<td>4.5</td>
</tr>
<tr>
<td>CREB</td>
<td>3.6</td>
</tr>
<tr>
<td>Cyt P450 51</td>
<td>3.4</td>
</tr>
<tr>
<td>Latent TGF-β-binding protein</td>
<td>7.5</td>
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<tr>
<td>65kd YES-associated protein</td>
<td>3.4</td>
</tr>
<tr>
<td>STRL22</td>
<td>3.9</td>
</tr>
<tr>
<td>Cell adhesion protein</td>
<td>5.9</td>
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<tr>
<td>Ribosomal proteins</td>
<td>3.7–8.1</td>
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<tr>
<td>Cytoplasmic antiproteinase</td>
<td>4.3</td>
</tr>
<tr>
<td>c-jun</td>
<td>3.0</td>
</tr>
<tr>
<td>ZFM1/B3</td>
<td>3.0</td>
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</table>

* cDNA array analysis before and 24 h after infusion of TPA revealed ≥3-fold induction of several genes in the primary leukemic cells from a patient with relapsed/refractory ANLL. No genes demonstrated ≥3-fold reduction of gene expression. No changes were detected in an identical analysis of another patient’s leukemic cells before and after administration of TPA.
on the ANLL cells of some patients. CD7 has been induced by TPA in cell lines and was detected in some patient samples. CD13, CD7, and CD14 appear to be modulated independently and without clear relation to the level of TPA-like activity in blood. It is currently unclear if the variability in immunophenotypic response to TPA reflects: (a) cellular heterogeneity with respect to genetic alterations and signaling pathway abnormalities; (b) low TPA doses used in this early part of the Phase I study; (c) metabolic parameters related to TPA or key metabolites; (d) variability in TPA-mediated effects on cytokine production, ANLL-stromal cell interactions, or other modulators of ANLL cell phenotype; or (e) other clinical, cellular, or biochemical features that cannot be detected at this early stage of the study. Ongoing studies of primary ANLL cells after ex vivo exposure to TPA will allow analysis of immunophenotypic effects at various doses in the absence of physiological and pathological variables such as metabolic parameters and controlled levels of cytokines/hormones. Ex vivo analysis is also important because analysis of cells in vivo may be compromised by the selection of cells over time (e.g., TPA-induced changes may result in subsets of cells leaving the circulation).

TPA-induced alterations in gene expression were detected by cDNA array analysis. Two patient samples were analyzed. The ANLL cells from 1 patient demonstrated induction of several genes 24 h after TPA exposure. For example, CREB and c-jun were induced, mimicking TPA-induced effects in many cell lines. In addition, genes related to signaling, adhesion, differentiation, chromatin remodeling, and cellular metabolism were induced. Hence, a broad spectrum of genes, whose products participate in diverse pathways, is induced. As more patient samples are analyzed at various times after TPA administration, it will be possible to use the cDNA arrays to identify coordinately regulated genes and cluster data based on clinical and biological parameters. This data will be used to generate testable mechanistic and therapeutic hypotheses and identify possible surrogate markers for specific TPA-induced biological outcomes.

The pattern of adverse effects seen was comparable with that detected in China. A striking degree of leukocyte activation is likely and may be responsible for some of the adverse effects. For example, one of our patients had a marked flare reaction of phlebitis when TPA was infused via a contralateral vein 7 days after the initial phlebitis. Other patients had fevers and dyspnea shortly after the infusion. These effects were transient and reversible. Macroscopic hematuria occurred in 2 patients; 1 patient required cystoscopy for evacuation of clots.

The intent of this report is to provide preliminary data that will support additional development of TPA and related compounds as therapeutic agents. The early results of our Phase I study indicate that TPA administration results in short-term/ reversible toxicity at doses that can induce phenotypic alterations of malignant cells and result in biological and clinical effects. Hence, these studies confirm the ability to treat patients with TPA and lay the foundation for the development of phorbol ester therapy for patients with a variety of malignant and nonmalignant disorders. Ongoing studies are assessing patterns of PKC and MAPK pathway activation, transcription factor activation, gene expression profiles, and induction of apoptosis in primary malignant cells after administration of TPA.

In summary, the broad spectrum of phorbol ester-inducible effects in cell lines raises the prospect for their development as therapeutic agents for a variety of malignant and nonmalignant disorders. However, there is little available data concerning in vivo effects of phorbol esters. Administration of TPA to patients with myeloid malignancies in China set the precedent for human studies and prompted the ongoing Phase I trial described in this report. To date, the major conclusions to be drawn from the Phase I study are: (a) administration of low doses of TPA to patients with relapsed refractory hematological malignancies results in an acceptable side effect profile similar to that described in China; (b) TPA-associated biological activity in blood can persist several hours after the administration of the drug; (c) TPA induces in vivo biological (and clinical) effects; and (d) there is interpatient variability in both in vivo and ex vivo effects of TPA on primary malignant cells. The capacity of TPA to induce biological effects at doses that result in reversible and tolerable adverse effects indicates the need for additional development of TPA.

REFERENCES


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