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Potential Chemotherapy Side Effects:

What Do Oncologists Tell Parents?

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Abstract

Background—In order to determine the number of short-term side effects and late effects discussed during an informed consent conference (ICC) after the diagnosis of acute leukemia, we observed the occurrence(s) and the ratio between short-term side effects versus late effects during an ICC.

Procedure—ICC(s) of childhood leukemia trials were audio-taped at six different study sites. The side effects mentioned during each of these ICC(s) were coded and analyzed.

Results—One hundred and forty cases were reviewed, from which we coded a total of 3173 acute side effects and 242 late effects. The mean total side effects mentioned during each ICC was 24 (range 5-47). The number of late effects coded were significantly less than acute side effects. We also found that the duration of ICC(s) was positively correlated with the number of side effects mentioned. In addition, the frequency of total side effects mentioned was independent of patient or parent demographic factors.

Conclusions—Our results show that acute side effects are often mentioned but the discussion of late effects is much less frequent in the initial ICC(s). Careful consideration regarding the ratio of acute and late effects that are communicated to parents in the context of the informed consent conference may facilitate parental understanding of clinically relevant side effects.

Keywords

chemotherapy side effects; late effects; physician-parent communication

INTRODUCTION

One significant challenge in the care of childhood cancer involves the communication of potential side effects that may be associated with the medical treatment of pediatric cancer to parents. Clear communication of acute side effects and late effects (i.e., those effects that may persist or arise post-treatment) of pediatric cancer treatment is necessary to help parents

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anticipate and understand the impact of their child's medical care. Oncologists face both the challenges of effectively treating cancer diagnosis while taking into account the considerable side effects caused by chemotherapeutic agents(1) as well as prioritizing long lists of major and minor side effects to describe and emphasize in their discussions with parents. Burdening parents who are distressed by their children's diagnosis with information about side effects, some of which may have low probability, may concern oncologists. Yet, concerns about burdening parents need to be weighed against the need to give parents comprehensive information about the potential acute side effects and late effects of their child's cancer treatment.

Several previous studies have described the communication of the diagnosis of pediatric cancer (2-5). In all of these studies, however, the potential acute side effects and late effects that were communicated to parents by oncologists were not observed directly and were based on parents' accounts. The potential discrepancies between what oncologists communicated about potential side effects of treatment and what parents remembered or understood, limits validity of information from previous studies. For this reason, data based on direct observation of the oncologists' communication to parents are needed. To our knowledge, no such observational study has been conducted. Such information is necessary to provide relevant guidance to oncologists while communicating therapy related acute side effects and late effects to parents. Physicians are most often the primary person who communicates therapy-related side effects to both patients and their parents. As public awareness of late effects continue to rise, the need to document physician communication of late effects discussion in these ICC(s) is heightened.

The present study employed a methodology that included direct observation and audio-taping of oncologists' communication about acute side effects and late effects during the informed consent conferences for pediatric leukemia treatment(6). These data were coded, then analyzed to describe the ratio of therapy-related acute side effects to late effects that were communicated to parents by oncologists. We also looked at the association between parent demographic characteristics and number of side effects discussed as well as duration of the informed consent conferences (ICC) as it relates to the number of side effects discussed.

METHODS

This study is part of a larger NCI-funded study entitled *Informed Consent in the Children's Cancer Group* which examined the informed consent process for participation in randomized clinical trials (RCTs) for treatment of pediatric leukemia. Participants were recruited from July 1, 1999 through December 31, 2001 at six CCG institutions: Rainbow Babies & Children's Hospital of University Hospitals of Cleveland in Cleveland, Ohio; Children's Hospital of Philadelphia in Philadelphia, Pennsylvania; Children's Hospital Medical Center in Cincinnati, Ohio; Children's Hospital of Los Angeles in Los Angeles, California; MD Anderson Cancer Center in Houston, Texas; and Children's National Medical Center in Washington, D.C.

The study was approved by Institutional Review Board at each site. Informed consent of the parents and physicians were obtained shortly after the patient's diagnosis with acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS). A total of 164 parents were asked to participate in this study, of which 140 (85%) consented. Trained research associates observed and audio taped the ICC(s) that physicians convened for the purposes of discussing the diagnosis and treatment options including RCT participation.

Data Reduction and Coding of Side Effects

The audio taped ICC(s) were transcribed into MS Word. Dialogue in Spanish was translated into English for the analyses. The transcripts were then imported into a NUD*IST Vivo (Nvivo) program for qualitative analysis. All 140 ICC(s) underwent three phases of analysis; the first two phases were systematically evaluated by a team of 8 coders (six undergraduates, two graduate students), the final phase was analyzed by a team of 4 coders (two oncologists, two graduate students).

During the first phase, all therapy-related side effects (both acute and late effects), were identified and coded within the Nvivo document. Following primary coding, transcripts were printed for secondary coding where all side effects (e.g., hair loss, nausea or hypoglycemia) were recorded along with the potential inciting agent. Subsequently, the data were loaded into an electronic database, where the presence of each side effect mentioned in each transcript could be recorded. Finally, all side effects were categorized, using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0(7) as a guide. When physicians described medical side effects with layperson language (e.g., lowered platelet count; puffy face, moon face, chipmunk cheeks, Buddha belly; foot drop; metallic mouth taste), the corresponding CTCAE terminology was applied (e.g., thrombocytopenia; cushingoid appearance; motor neuropathy; dysgeusia) for categorization.

Statistical Analysis

In this study, we defined acute side effects of chemotherapy as reversible adverse events that occurs secondary to administration of chemotherapy. Late effects were quantified as long term; non-reversible treatment related side effects that become apparent after completion of cancer therapy. We tabulated all side effects and classified them into two categories; acute side effects and late effects.

Pearson's correlations were computed to evaluate continuously measured factors associated with number of side effects mentioned in each of these ICC(s). Analysis of variance and t-tests were used to test for associations between parent demographics and number of side effects. The level of statistical significance for all of our analyses was set at $p<0.05$.

RESULTS

Patient and Parent Characteristics

As shown in table 1, study participants included 140 parents of children diagnosed with acute leukemia. The majority of parents (61%) were female. Fifty-six percent of parents were Caucasian, and the remaining were ethnic minorities. Among the patients diagnosed with acute leukemia, the mean age was 7 years (SD= 7.6), and majority of them were males. We used the Hollingshead 5-point Index of Social Position (ISP)(8) to measure socioeconomic status (SES) of parents within this study. A lower ISP score represents a higher SES. Forty one percent of parents had a ISP score of 4-5(8) reflecting low SES. All of the patients diagnosed with acute leukemia were enrolled in one of the four Children's Cancer Group (CCG) leukemia trials as shown in Table II.

Ratio of acute side effects versus late effects

A total of 3173 acute side effects (Table III) were reported in all one hundred and forty cases in our study. In contrast, only 242 late effects (Table IV) were observed in these ICC(s). This represents a 13:1 ratio of acute to late effects discussed by oncologists in the initial ICC(s).

Factors associated with number of side effects discussed

The mean number of total side effects (acute and late effects) mentioned per case was 24 (range 5-47; SD= 9.14). Mean number of acute side effects per case was 23 (range 5-45; SD= 8.315) while only 2 late effects per case (range 0-7; SD= 1.549) were observed on average. Parent age ($r = .11$, $p = 0.19$), gender, ethnicity and socioeconomic status were not associated with the number of side effects discussed during these initial ICC(s). While 26% parents were Hispanic, only 25 out of 140 ICC(s) were conducted in Spanish with the presence of an interpreter. Our analysis showed that the presence or absence of an interpreter does not affect the number of side effects mentioned during the ICC(s) (Table V). Length of ICC(s) was positively correlated with the number of total side effects discussed ($r = .26$, $p = .002$). The number of total side effects mentioned was negatively correlated with oncologists' years of clinical experience ($r = -.23$, $p = .006$), albeit a small effect size. This finding was also true for the number of acute side effects mentioned ($r = -.23$, $p = .008$) but was not for late effects ($r = -.15$, $p = .076$).

Discussion

We believe that the present study is the first to describe direct observation of the discussion of therapy related acute side effects and late effects between oncologists and parents of children newly diagnosed with cancer. The therapy of children diagnosed with acute leukemia consists of multiple different anti-neoplastic agents, all of which can cause potential side effects. These adverse effects may occur early during therapy or after completion of therapy. Although many of the side effects are short-lived and reversible, others can be permanent and cause long term physical and or psychological problems in these patients (i.e. late effects). Consequently, oncologists are constantly placed in a dilemma of deciding which among many side effects to discuss with these families.

Over the past decade, communication skills have received much attention as a tool in clinical oncology. Many have tried to develop training techniques to improve physician-patient communication with varying results (9). Nonetheless, most oncologists do not receive any formal training on discussion of side effects with parents. This challenge for oncologists is compounded by the fact that each physician has to decide which side effects among the many to disclose to parents. There is a natural tension between the need to focus on side effects which are common and the need to disclose side effects which may be infrequent but are severe. Similarly, a dilemma concerning the need to disclose potential acute toxicities versus late effects also exists. Moreover, there are no guidelines or literature to suggest the actual number of appropriate side effects to disclose to parents. For these reasons, data from our study can serve as a normative guide for oncologists to present information to parents.

Our study reported a total of 3713 acute side effects and 242 late effects in all one hundred and forty ICC(s). This shows that oncologists are discussing and warning parents of acute adverse events that their children may suffer as a result of therapy. Our results showed that oncologists tended to focus on high probability and observable side effects (e.g., nausea, hair loss, changes in appetite) in over 85% of conferences, while lower probability and potentially more serious side effects (e.g., appendicitis, arthritis, thyroid damage) were mentioned in less than 1% of cases.

Strikingly, the ratio of acute side effects to late effects was 13:1, with a mean of 2 late effects mentioned per ICC. It may be the case that this unbalanced ratio is a reflection of the fact that there are many more possible acute side effects than late effects. However, this ratio may suggest that oncologists should reconsider the way they discuss therapy-related late effects and include more late effects in their discussions in order to inform parents more

completely about them. Multiple previous studies on adult patients have shown that most patients would like to know more if not all possible side effects that may occur as a result of their therapy (10-12). Although it is impossible to discuss all potential acute side effects and late effects with parents, especially during the stressful time of new diagnosis, our data may prompt oncologists to consider an increased focus on potential late effects from the outset.

We analyzed different factors that may affect the number of side effects mentioned in these ICC(s) and found that the number of all side effects (acute or late effects) discussed were independent of parent age, gender, ethnicity and socioeconomic status. Interpreters play a large role during ICC(s) with families who have limited English proficiency (13). Since there is a sizeable ethnic population within our study, we analyzed for differences between the number of side effects mentioned in ICC(s) with and without the presence of an interpreter. Our data suggests that there were no differences between the number of side effects discussed when an interpreter is present during the ICC (s).

One of the variables that were positively correlated with number of side effects mentioned was the length of the ICC. Even though the informed consent process is time consuming, this finding showed that the time spent with these parents may be justified because more information was conveyed to the parents when the duration of the ICC(s) was longer. Findings from our study also showed that oncologists with fewer years of clinical experience tend to discuss more side effects to parents when compared to their more experienced counterparts. The implication of this finding remains unknown, but one might speculate that the confidence that comes with years of clinical experience prevents the seasoned clinician from feeling the need for an exhaustive disclosure of potential toxicities. It should also be noted that the effect size of this finding was relatively small.

The main limitation of this study is that the audio-taped communication we analyzed represented the initial ICC(s) subsequent to the patients' diagnoses of acute leukemia. Because informed consent is a process, we cannot account for the number of side effects discussed beyond the audio-taped portion of the ICC(s). Similarly, we did not review the written consent document so could not include side effects that were disclosed in writing (but not verbally) in this analysis. Studies have shown poor parent recall of ICC content, especially during the initial ICC(s) when parents and their newly diagnosed children are going through a difficult and stressful time (14-15). For this reason, it is difficult to assess how much of these discussions of adverse events were retained by parents shortly after the ICC. Since the treatment of childhood cancer has a prolonged course, parents often go through repeated discussions of treatment and side effects throughout their child's course of therapy. Many oncologists may choose to discuss late effects during the subsequent ICC(s) or even toward the end of therapy. Nevertheless, the early discussion of late effects is important, as it allows parents to gather information and anticipate what their child may encounter when they are in remission. A final potential limitation is that acute side effects may have been subcategorized while late effects were described more generally. If this was the case, it would distort the ratio of acute versus late effects disclosed.

Future research regarding communication of pediatric cancer treatment side effects is needed. Such research should focus on the relationship of parental distress to the breadth and content of the discussion. It should also assess physician and parent attitudes in determining which side effects are necessary to communicate to parents in the earliest phases of the therapeutic relationship. Parents who have recently learned that their child has leukemia will appreciate thoughtful attention to the complexities surrounding communication of toxicity risk during this critical time period.

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Table I

Parent and Child Characteristics

			Mean (SD)
Age	Parent:		35 (4.7)
	Patient:		7 (7.6)
Gender	Parent:	Male	55 (39%)
		Female	84 (61%)
	Patient:	Male	80 (57%)
		Female	60 (43%)
Race	Parent:	White	79 (56%)
		Black	13 (9%)
		Hispanic	36 (26%)
		Asian	6 (4%)
		Other	6 (4%)
Parent ISP* †	1-2		34 (24%)
	3		48 (34%)
	4-5		57 (41%)
Child Diagnoses	ALL		125 (89%)
	AML		14 (10%)
	MDS		1 (0.7%)

ALL = Acute lymphoblastic leukemia, AML = Acute myeloid leukemia, MDS = Myelodysplastic syndrome

† One missing data

* Abbreviation: ISP, Hollingshead Index of Social Position. Socioeconomic status was measured by the ISP which assigns socioeconomic status (SES) using education and occupation. On this scale of 1-5, a lower ISP score represents a higher SES; N = 140

Table II

Distribution of patients according to respective leukemia protocol

Protocol	Frequency (N)	Percentage (%)	Chemotherapeutic agents used in each study protocol
CCG1952	24	17	Vincristine
			Dexamethasone/Prednisone
			Asparaginase
			Doxorubicin
			Cyclophosphamide
			Methotrexate (IT/PO)
			Cyclophosphamide
			Cytarabine
			Mercaptopurine/Thioguanine
CCG1991	36	26	Vincristine
			Daunomycin
			Dexamethasone
			L-Asparaginase/PEG-Asparaginase
			Methotrexate (IT/PO/IV)
			Mercaptopurine
			Cyclophosphamide
			Doxorubicin
			Daunorubicin
			Thioguanine
CCG1961	65	46	Vincristine
			Prednisone/Dexamethasone
			L-Asparaginase/PEG-Asparaginase
			Methotredxate (IT/PO)
			Cytarabine (IT)
			Daunomycin/Adriamycin/Idarubicin
			Mercaptopurine
			Thioguanine
			Cyclophosphamide
CCG2961	15	11	L-Asparaginase
			Cytarabine
			Daunomycin
			Dexamethasone
			Etoposide
			Fludarabine
			Idarubicin
			Hydrocortisone (IT)
			Inteleukin-2

Protocol	Frequency (N)	Percentage (%)	Chemotherapeutic agents used in each study protocol
			Methotrexate
			Thioguanine

Table III

Acute Side Effects Mentioned by Oncologists

Category	Frequency
Allergy/Immunology	**97**
Allergic Reaction	93
Anaphylactic Shock	4
Blood/Bone Marrow	**380**
Anemia (Hemoglobin)	90
Bone Marrow Suppression	103
Leukopenia	90
Thrombocytopenia	97
Cardiac	**177**
Cardiac Dysfunction	86
Changes in Blood Pressure	91
Coagulation	**72**
Clotting Problems	72
Constitutional Symptoms	**176**
Bloating/Fluid Retention	50
Body Temp Disregulation (chills, fever)	54
Weight Gain	70
Weight Loss	2
Dermatology/Skin	**251**
Alopecia	127
Hair and Nail Changes	9
Injection site reaction	34
Skin Disturbances (bruising, scratches, blemishes, discoloration)	69
Striae	1
Flushing	7
Photosensitivity	4
Endocrine	**150**
Cushingoid Appearance	37
Glucose Intolerance/Hyperglycemia	104
Hypothyroidism	1
Polydypsia	8
Gastrointestinal	**626**
Appendicitis	2
Appetite Changes	119
Constipation	98
Diarrhea	44

Category	Frequency
Dysgeusia	4
Gastrointestinal Tract Problems	57
Increased Fat Intake	3
Nausea/Vomiting	123
Splenomegaly	1
Abdominal Pain/Cramping	77
Mucositis/Stomatitis	98
Hemorrhage/Bleeding	**79**
Susceptibility to Bleeding	79
Hepatobiliary/Pancreas	**158**
Liver Dysfunction/Failure	77
Pancreatitis	81
Infection	**121**
Dental/Periodontal Infection	1
Infectious Risks	114
Lymphadenopathy	6
Musculoskeletal/Soft Tissue	**6**
Avascular Necrosis	5
Arthritis	1
Neurology	**402**
Ataxia	26
Central Nervous System Complications and Stroke	41
Cognitive Changes/disturbances	14
Hyperactivity	1
Mood Swings/Changes	95
Motor Neuropathy	35
Sensory Neuropathy	89
Sleep Disturbances	38
Temporary Psychosis (Hallucinations)	3
Seizures/Convulsions	60
Ocular/Vision	**37**
Vision Changes, Eye Pain/Pressure	36
Conjuctivitis	1
Pain	**248**
Back Pain	7
Bone pain	19
Ear Pain	2
Headaches	51
Jaw Pain	87

Category	Frequency
Lower Extremity Pain	60
Neck pain	12
Upper Extremity Pain	10
Pulmonary/Upper respiratory	**39**
Pneumonitis	2
Shortness of Breath	36
Voice changes (Hoarseness)	1
Renal/Genitourinary	**119**
Cystitis	43
Urine Discoloration	12
Polyuria	12
Renal Functioning/Failure	52
Syndromes	**35**
“Flu-like” Symptoms	35
Total Acute Side Effects	**3173**

N=140

Table IV

Late Effects Mentioned by Oncologists, N = 140

Category	Frequency
Chronic Health Conditions	**210**
Amenorrhea	3
Brain Damage	30
Cardiomyopathy	47
Growth and Developmental Delay	12
Infertility	43
Learning Difficulties/Disabilities	28
Osteoporosis	47
Secondary Malignancy	**30**
Secondary Malignancy	30
Mortality	**2**
Death	2
Total Late Effects	**242**

Table V

Association of parent demographic and number of side effects discussed

Parent Demographics		Mean side effects discussed	Standard Deviation	Probability (p<)
Gender	Male	24.11	9.62	0.744
	Female	24.63	8.91	
Ethnicity	White	23.91	9.32	0.678
	Black	22.69	7.70	
	Hispanic	25.31	9.03	
	Asian	28.67	11.30	
	Other	24.67	9.33	
Interpreter	Present	27.04	10.27	0.110
	Not present	23.82	8.82	
ISP*	1-2	23.76	8.60	0.847
	3	24.92	8.38	
	4-5	24.21	10.20	

*Abbreviation: ISP, Hollingshead Index of Social Position. Socioeconomic status was measured by the ISP which assigns socioeconomic status (SES) using education and occupation. On this scale of 1-5, a lower ISP score represents a higher SES.