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STATE-OF-THE-ART IN THE MANAGEMENT OF CANCER

BREAST CANCER–PART II ASYMPTOMATIC POPULATION SCREENING AND SUSCEPTIBILITY TESTING

Overall improvement in survival rates of patients with breast cancer in the last two decades is commonly attributed to early diagnosis of disease by effective and aggressive screening programs of asymptomatic populations based on self examination, clinical vigilance and mammography. Despite continued increases of incidence rates of breast cancer in this period, which may be attributed to patient education regarding self examination and adoption of screening programs, early disease detection has improved five-year survival; in the USA, five-year survival rates rose from 74.9% in 1975 to 83.2% in 1995.

BREAST SELF EXAMINATION

Breast self examination (BSE) ushered in the era of mass screening for the detection of breast cancer. Although BSE has been overshadowed by mass mammography screening in many Western countries, it is still considered a very effective detection method that when used properly may identify early asymptomatic disease. However, results of a randomized clinical trial, involving 120,310 Russian women aged 40-64 years with no history of breast cancer, initiated under the auspices of the World Health Organization (WHO) in 1985, did not show any difference in the size and stage of the detected tumors (190) in the BSE group, compared to those (192) among controls. However, women performing BSE were more likely to visit their physician with breast "pathology" complaints and undergo more biopsies for benign lesions. This study is ongoing and information on mortality should be available after 1999 (Semiglazov VF, etal, Eur J Epidemiology, July 1992, 8(4):498-502).

This trial demonstrated the problems encountered with BSE regarding compliance; the percentage of those performing BSE dropped from 82 at entry to 55.8 at the time of the above review, while only 17.9% of women performed monthly BSE, compared to 55.8% at entry. However, other studies demonstrated that instruction improves the rate of BSE. In the Canadian National Breast Screening Study (CNBSS), BSE behavior was analyzed in 89,835 participants. At entry, approximately 20% reported performing BSE 12 times a year or more frequently. At final screen, this ratio increased to 64% and 50%, respectively, and 50% zero frequency of BSE at entry was reduced to 10% (Baines CJ and To T, Cancer, 1 Aug 1990, 66:570-6).

Inventive Products

Inventive Products (Decatur, IL) has developed Sensor Pad, a BSE aid used as an alternative to soap and water to reduce friction between the fingers and the breast allowing a smooth motion and enhancing the sense of touch. Approved by the FDA in late 1995 for BSE and available by prescription, Sensor Pad consists of silicone lubricant sealed between two 10-inch circles of polyurethane. When placed upon the breast the top layer, manipulated by the user's fingers, moves freely over the bottom layer facilitating identification of any abnormalities. In the USA, Sensor Pad is mainly sold to hospitals at a price of $19.95. It has also been approved in Europe and Japan.

BREAST CANCER SCREENING BASED ON MAMMOGRAPHY

Mammography is currently routinely implemented as a screening tool for the early detection of breast cancer and represents the largest screening effort ever undertaken in the USA for any type of cancer. Although mammography is credited with early diagnosis of breast cancer and, therefore, higher survival rates, universal screening using this approach has its detractors. Those who embrace mammography screening have many reasons to be convinced of its benefits that seem to be proven by countless studies undertaken to assess the impact of mammography in women over the age of fifty, among them several randomized controlled trials summarized in Exhibit 1, which involved over 231,000 women. Results demonstrate a 25-30% reduction in mortality rates in women aged 50-74. The undeniable benefit of regular screening in this age group is almost universally acknowledged and has led to the implementation of nationwide screening programs in several countries, including the USA, Canada, Sweden, the Netherlands, Denmark, Finland, and the UK.

Based on results from these randomized trials, organizations around the world began making or revising recommendations for breast cancer screening. In general, most agree that annual breast cancer screening with mammography alone or mammography and clinical breast examination (CBE) in women over age 50 is beneficial. This resulted in a rapid increase in mammography rates in North America and Western Europe (see Exhibit 2). The number of procedures (both diagnostic and screening) performed in the USA grew from 11.8 million in 1988 to 15.5 million in 1990, to 22.0 million in 1992, and to 24.5 million in 1994. Based on this trend, it is estimated that approximately 25.5 million procedures were performed in the USA in 1995 and that 45.5% of all women over age 50 had a mammography in 1995. The national health objective for the year 2000 is to screen 60% of women >50 years, every two years. The Centers for Disease Control (CDC) estimate that in 1992 (the most recent year for which actual survey data is available) 44% of women over the age of 50 were screened with mammography every two years. The overall goal is to screen 80% of women > 40 years at least once; in 1992, 70% and in 1995, 75% of these women were screened at

Exhibit 1
Randomized Clinical Trials in Mammography Screening

Trial	Period	Age at entry	Follow-up (years)	Mortality (%)[6]	Relative Risk (95% CI) > 50 years	Relative Risk (95% CI) < 50 years
HIP[1] (USA)	1963-69	40-64	10	-23	0.68 (0.49-0.96)	0.77 (0.50-1.16)
Kopparberg[2] (Sweden)	1977-85	40-74	12	-27	0.67 (0.50-0.90)	0.75 (0.41-1.36)
Ostergotland[2] (Sweden)	1977-85	40-74	12	+2	0.75 (0.57-0.99)	1.28 (0.70-2.33)
Malmo (Sweden)	1976-86	45-69	12	-49	0.86 (0.64-1.16)	0.51 (0.22-1.17)
Stockholm (Sweden)	1981-85	40-64	8	+4	0.65 (0.40-1.08)	1.04 (0.53-2.05)
Gothenborg (Sweden)	1982-88	40-59	7	-40	0.91 (0.53-1.55)	0.73 (0.27-1.97)
Edinburgh[3] (UK)	1979-88	45-64	10	-22	0.85 (0.63-1.14)	0.86 (0.41-1.80)
Canada 1[4]	1980	40-49	7	–	–	1.36 (0.84-2.21)
Canada 2[4]	1980	50-59	7	–	0.97 (0.62-1.52)	–

[1]At 18 years from entry; relative risk for all ages was 0.77 (0.61-0.97) [2]Two county Swedish trial [3]Preliminary data presented at the International Workshop on Screening for Breast Cancer, February 24-25, 1993 [4]Canadian National Breast Screening Study (CNBSS); comparison is between mammography plus clinical breast exam versus clinical breast exam alone at initial screening [6]Based on meta-analysis

least once in their lifetime. Recommendations regarding screening women older than 74 have not been proposed. Increases in mammography rates are also estimated for countries which have nationwide screening programs as well as those with national health care delivery systems. The number of mammography procedures for 1995 in these countries, estimated in Exhibit 2, is based on USA rates (see footnote) because reported figures from around the world are not available for recent years. In countries that do not have well established national health care or screening programs (e.g. Eastern Europe), it is reasonable to expect that most of the mammographies are performed for diagnostic rather than screening purposes.

Despite widespread use, mammography screening of asymptomatic populations remains controversial. Those who question the value of mammography screening argue that:

- in order to achieve one less death per year, between 7,086 women (based on the HIP study results) and 63,264 women (based on the Malmo, Sweden study results) would have to be screened at a cost between $500,000 and $4.4 million (Wright CJ and Mueller CB, The Lancet, 1 July 1995, 346:29-32); others estimate that the cost per year-of-life-saved is $20,000 for those between the ages of 40-49 screened on an annual basis and $125,000 for those between the ages of 40 and 64
- of the 5% positive mammograms (1.25 million in the USA alone), 80-93% are negative at biopsy, exposing women to unnecessary invasive procedures, anxiety and cost
- as many as 33% of mammograms cannot be interpreted, requiring repeat procedures and additional costs
- unlike the situation in highly controlled clinical trials, many mammograms are incorrectly interpreted in the real world, diluting the effect of mass screening
- when all is taken into consideration the cost of one life saved by mass mammography screening exceeds $1 million

In addition to RCTs, many epidemiological studies and testing programs have provided valuable data regarding mammographic screening. In the USA, the Breast Cancer Detection Demonstration Project (BCDDP), jointly funded by the American Cancer Society (ACS) and the National Cancer Institute (NCI), screened 280,000 women between the ages of 35 and 74 years in the 1973-1982 period. Also, under the auspices of the CDC's National Breast and Cervical Cancer Early Detection Program, mandated by the Breast and Cancer Mortality Prevention Act of 1990, 327,017 mammograms were performed between July 1991 and September 1995. Of these 61.2% were performed in women aged ≥50 years and 46.7% in racial and ethnic minorities. Although the rate of abnormalities were highest in younger women, the rate of breast cancer detected increased directly with increasing age from about 400 per 100,000 mammograms among those aged 40-49 years to double that rate for those over 75 years-of-age.

Mammography Screening for Women Aged 40-49 Years

The usefulness of screening using mammography in detecting breast cancer in younger women is a much debated issue. Only four of the eight RCTs listed in Exhibit 1, showed a decrease in mortality in this age group but none of the observed reductions were statistically significant. In addition, reduction in mortality was observed only after 10-12 years whereas in women over 50 years-of-age such decreases were seen after only six years. Reasons for this variation with length of follow-up in

Exhibit 2
Estimated Mammography Procedures in Selected World Regions in 1995

Country	Age 40-49 Procedures (#)	Age 50-59 Procedures (#)	Age 60-69 Procedures (#)	Age 70-79 Procedures (#)	Age 80+ Procedures (#)	Age > 40 Procedures (#)
Greece[1]	191,800	227,150	214,080	110,880	40,860	784,770
Ireland[1]	63,000	56,700	42,560	31,080	9,540	202,880
Italy[1]	1,073,800	1,250,550	1,088,960	670,320	250,020	4,333,650
Portugal[1]	175,840	195,650	173,440	106,680	32,580	684,190
Spain[1]	694,960	741,650	705,600	440,720	147,780	2,730,710
Belgium[2]	234,630	219,200	208,310	138,270	58,880	859,290
Germany[2]	1,822,800	2,214,000	1,650,940	1,140,480	526,470	7,354,690
Luxembourg[3]	10,640	10,800	9,240	5,400	2,700	38,780
France[3]	1,586,500	1,298,700	1,261,260	770,760	463,800	5,381,020
Denmark[4]	162,970	160,650	116,640	87,330	45,500	573,090
Netherlands[4]	495,360	419,220	332,160	228,370	114,450	1,589,560
United Kingdom[4]	1,693,770	1,615,680	1,344,960	972,110	544,600	6,171,120
EEC Total	8,206,070	8,409,950	7,148,150	4,702,400	2,237,180	30,703,750
Malta[1]	6,720	7,590	7,360	3,920	1,440	27,030
Austria[3]	196,840	212,850	162,540	126,720	60,300	759,250
Finland[3]	157,320	131,400	109,200	75,240	33,900	507,060
Iceland[3]	6,460	5,400	4,200	2,880	1,200	20,140
Norway[4]	129,430	111,180	90,240	78,720	39,900	449,470
Sweden[4]	263,160	261,120	200,640	166,870	91,000	982,790
Switzerland[4]	217,580	214,200	164,160	109,880	63,700	769,520
Non-EEC Total	977,510	943,740	738,340	564,230	291,440	3,515,260
Eastern Europe Total[5]	1,352,690	1,176,400	988,550	514,950	156,500	4,189,090
Europe* Total	10,536,270	10,530,090	8,875,040	5,781,580	2,685,120	38,408,100
USSR Total[5]	3,264,680	3,155,800	2,638,910	1,344,450	455,400	10,859,240
Japan[4]	4,195,510	2,810,610	3,455,520	1,917,570	835,100	13,214,310
United States	8,252,990	6,523,920	5,120,640	3,705,170	1,892,450	25,495,170
Canada[4]	973,950	766,020	580,320	394,830	193,550	2,908,670
North America	9,226,940	7,289,940	5,700,960	4,100,000	2,086,000	28,403,840
Triad (Europe,* Japan, NA)	23,958,720	20,630,640	18,031,520	11,799,150	5,606,220	80,026,250
TOTAL	28,811,710	25,064,850	21,617,950	13,729,160	6,263,170	95,486,840

*Note: Estimates based on mammography rates in the USA in [1]1990; [2]1992; [3]1994; [4]1995; [5]1987 * Excluding the former USSR*

women aged 40-49 include the possibility that breast cancer in these women did not occur until after they were 50 years-of-age or older. Furthermore, younger women may be more likely to have indolent tumors which progress slowly, hence the reduction in mortality is delayed (Esserman L and Kerlikowske K, Oncology, March 1996; 10 (3):357-364). Although some have argued that mammography may not be as sensitive in younger women because their breasts are more glandular and dense, improvements in mammographic techniques have greatly increased the sensitivity of mammograms in younger women. A recent study concluded that over 90% of breast tumors are detectable by mammography in women 40-49 years today compared with 38% in the HIP study.

There is also general consensus that women under age 40 should not undergo routine screening unless they are considered high risk because of family history, previous cancer and atypia, among others. However, recommendations for women ages 40-49 vary widely. Proponents argue that the potential life-saving benefits of routine screening are significant even if they occur after many years. Those against it cite the economic burden of unnecessary screening and the general lack of scientific evidence to justify routine screening. The ACS, American

College of Radiologists (ACR), American Medical Association (AMA), American College of Obstetrics and Gynecology (ACOG), Australia, and Iceland recommend either annual or biennial mammography for women aged 40-49. However, the American College of Physicians (ACP), American Academy of Family Physicians (AAFP), U.S. Preventive Services Task Force, NCI, Canadian Task Force, United Kingdom, Finland, and Sweden do not recommend routine screening in asymptomatic women in that age group. Other areas of disagreement include screening frequency (annual versus biennial) and the combination of tests (mammography, CBE, and BSE) to be used. In March 1996, a re-analysis of the data from the five randomized Swedish trials reported a statistically significant 23% overall reduction in mortality in women 40-49 years who were screened with mammography. This has prompted the NCI to plan a consensus conference in late 1996 to re-examine this issue.

Problems Associated with Mammography

Although responsible for identifying early cancer and probably saving the lives and sparing the breasts of many women, mammography has also resulted in thousands of cases of unnecessary biopsies. Actually, standard mammography is impossible to interpret in 33% of cases (25% attributed to radiologically dense breasts and the remaining 7% to previous scarring, implants, among others). Interpretation of mammograms also suffers in the hands of radiologists. A British study that compared results of reading of mammograms by a single radiologist with reading by two radiologists, based either on a consensus (both radiologists agree on either recalling or referring cases to a senior radiologist) or non-consensus (either may recall cases) approach, concluded that consensus-double reading was the most effective. In the consensus mode, radiologists detected 80 cases of cancer from 10,000 mammograms compared to 71 by a single reading; also consensus reading was associated with the lowest patient recall (4.2%) for further assessment, compared with 6.9% for non-consensus reading and 9.9% for single reading. Consensus reading costs were significantly lower than either of the other two methods (Brown J, etal, BMJ, 30 Mar 1996, 312:809-12).

Numerous new developments, to be discussed in Part III of this report, promise to introduce less traumatic techniques to identify benign disease and to render screening and diagnostic mammography easier to interpret and more reliable.

Mammography Screening Costs

In contrast to rates, the cost of mammography has decreased over the past five years. Medicare, which began reimbursement for screening in 1991, paid approximately $61 per exam in 1995. The NCI reported that the current cost of a mammogram nationwide ranges between $35-$225 (average $70) compared with an average of $104 in 1990 and $89 in 1992. Based on the average rate of $70 per procedure, in the USA alone the cost of mammography screening is estimated at $1,784 million in 1995.

GENETIC SUSCEPTIBILITY SCREENING

Genetic susceptibility screening is one of the newest and probably one of the most powerful screening modalities in identifying individuals at risk for a given disease. At the same time, testing individuals for genetic traits that may predispose them to disease is a novel idea whose time may not have come. In many cases, identifying such populations may only lead to lifelong anxiety about the specter of a life-threatening disease that may never happen or for which no effective early intervention exists and, possibly, stigmatize a segment of the population that may then be denied insurance or employment, creating yet another underclass. As more and more genetic markers are identified that are shown to predispose their hosts to serious diseases, the controversy of susceptibility testing is expected to intensify.

In view of this, the NCI is planning to create the Cancer Genetics Network to study genetic susceptibility to cancer and the role of gene-environmental interactions in the development of cancer. However, because screening for genetic susceptibility to cancer and the creation of a registry of mutation carriers is a highly controversial issue, it is unlikely that such programs will be set in motion before enforceable laws to protect the privacy of those tested are in place that will shield those found to carry relevant mutations from all kinds of discrimination. For now, consumer groups are expected to support a national effort to identify and follow mutation carriers only if the aim of the program is to study how environmental or other variables promote carcinogenesis in these cases and how to prevent them and not if the goal is to identify carriers and study their outcome, at least until an effective intervention becomes available.

One step in the right direction has been passage on August 21, 1996, of the Health Insurance Portability and Accountability Act of 1996 (Public Law 104-191) that prohibits discrimination, through exclusion or higher premiums, against individuals based on health status, including genetic information. The law mandates that genetic information may not be treated as a pre-existing condition in the absence of a definite diagnosis.

Susceptibility Screening in Breast Cancer

Genetic susceptibility testing has become an immediate real issue in breast cancer because of the identification of BRCA1 and BRCA2 genes that have been shown to be hereditary markers that predispose women to the disease (see FO, V2 #4, pp 337-339). Many health organizations are beginning to establish clinical practice guidelines to implement genetic susceptibility testing, in general, and BRCA1 and BRCA2 testing, in particular. Kaiser Permanente (Oakland, CA) is planning to establish a confidential in-house BRCA1 registry. Also, the

American Society of Clinical Oncology (ASCO) recently issued genetic testing guidelines.

Currently, breast cancer susceptibility screening is provided in few settings, mostly reference laboratories, in conjunction with pre- and post-test counseling and comprehensive informed consent. Targeted populations include women who have been diagnosed with breast cancer and high risk individuals with a family history of early-onset breast cancer. Although considered predictive, presence of BRCA1 mutations is also useful in evaluating the course of the disease in women already diagnosed with breast cancer. Those positive for BRCA1 mutations run a 50% to 60% risk of developing cancer in the other breast. Also, interestingly, approximately 1% to 19% of women testing positive for BRCA1 mutations, get cancer even after they undergo prophylactic mastectomies.

Unlike periodic screening, susceptibility testing is only performed once but it is currently costly, estimated at between $300 for detection of one mutation to $1,500 for profiling the whole gene. Tests are complex to perform, taking 2-8 weeks, but the process is expected to be simplified when test kits enter the market. Currently, third-party reimbursement for genetic susceptibility screening is not widely available. *In vitro* tests to screen large populations for markers that predispose to cancer and/or detect malignancy represent a unique worldwide market opportunity. However, unlike prostate cancer for which a blood test, prostate-specific antigen (PSA) exists, no such testing approach is currently available for breast cancer.

Myriad Genetics (Salt Lake City, UT), through its wholly owned subsidiary, Myriad Genetic Laboratory, has obtained permits to conduct BRCA1 testing, under the brand name BRACAone, in all 50 states and plans to also offer a combination BRCA1/BRCA2 testing service in 1997. Myriad is collaborating with Eli Lilly in this area (see FO, V2 #4, pp 337).

OncorMed (Gaithersburg, MD) has been offering BRCA1 testing at its reference laboratories for the past couple of years. The company combines testing with its own counseling service.

Visible Genetics (Toronto, Canada) is using its DNA sequencer to conduct fragment analysis and to locate point mutations in BRCA1 in order to develop an automatic testing method to screen for the gene.

Editor's note: *Parts III and IV of this article will describe products and techniques used in diagnosis, staging, prognosis, monitoring and treatment of breast cancer, including in vitro diagnostics and in vivo imaging techniques, biopsy, surgical, radiation and chemotherapy options, current worldwide drug markets, and novel treatment approaches, including a database of over 100 agents in development.*

MEETING COVERAGE

NEW DEVELOPMENTS IN THE TREATMENT OF AIDS-ASSOCIATED KAPOSI'S SARCOMA

FROM THE XI INTERNATIONAL AIDS CONFERENCE, VANCOUVER, BC, CANADA JULY 7-12, 1996

EPIDEMIOLOGY

Kaposi's sarcoma (KS), first described in 1872 by the Austro-Hungarian dermatologist, Moritz Kaposi, comprises several different forms of the disease. The disseminated, fulminant form of KS associated with HIV infection, first observed in 1981 in young homosexual or bisexual men, is referred to as epidemic KS to distinguish it from the classic, African, and transplant-associated indolent varieties of this neoplasm. KS has also been identified in HIV-negative homosexual men.

In general, the risk of contracting AIDS-associated KS (AIDS-KS) is greater among those who acquired HIV by sexual contact than parenterally, and is 10 times more common in homosexual men than in other HIV+ men. Approximately 95% of all cases of epidemic KS in the USA have been diagnosed in homosexual or bisexual men. Almost 26% of all homosexual HIV+ males present with KS at first diagnosis, or will eventually develop it during the course of their illness. In comparison, less than 3% of all HIV+ heterosexual intravenous drug users (IVDUs) develop KS. KS is even rarer in other AIDS groups (women; those acquiring HIV infection through blood products). In Africa, where most HIV is contracted via heterosexual sex, the male to female ratio of AIDS-KS-afflicted individuals is 3:1. This would indicate a predilection in males or a protective effect in females which may be attributed to sex hormones.

During the past decade, incidence of KS presenting as a first AIDS-defining event has declined from 40% to 15%. In 1981, about 48% of AIDS patients had KS as their presenting illness; by August 1987, the cumulative proportion of AIDS patients who presented with KS had diminished to less than 20%, perhaps as a result of changes in the CDC AIDS definition instituted in 1987. In New York City, KS was the initial AIDS diagnosis in 50% of non-IVDU homosexual men in the 1981-1983 period; from 1984 to 1987, this proportion fell to 30%. This decline may not be fully attributable to the broadening CDC definition of AIDS but may reflect a decline in sexual transmission of HIV as a result of safe sex practices.

It is currently estimated that there are approximately 18,000-20,000 AIDS patients with diagnosed epidemic KS in the USA and probably 12,000-15,000 in Europe, bringing the total to about 30,000-35,000 patients. Incidence of diagnosed AIDS-KS is estimated at 2,700 annually in the USA and about 2, 000 in Europe, for a total of 4,700 newly diagnosed cases. Prevalence of AIDS-KS may

have reached a steady state with those dying with the disease being replaced with newly diagnosed cases. Prevalence may also drop in the future as new HIV treatments appear to be more effective in delaying advanced disease and its complications, including AID-KS.

ETIOLOGY

The etiology of AIDS-KS remains obscure. It has been suggested that HIV, in addition to promoting progression of KS via suppression of the immune system, may itself play a more direct role in the development of KS. For instance, the Tat protein of HIV, released from cells, may promote formation of KS-like lesions via interactions with basic fibroblast growth factor (bFGF). However, gay men who are not infected with HIV also contract a type of KS indicating that another causative factor may be at play. Also, in a phase I trial, Ro 24-7429 (Hoffmann-La Roche), a chemical inhibitor of Tat, was not shown effective against AIDS-KS. One other possible etiologic factor is KS-associated herpesvirus (KSHV), or human herpesvirus 8 (HHV8), originally identified in 1994. The possible role of a sexually transmissible agent was suggested by several epidemiologic observations:

- researchers have reported occurrence of KS in an increasingly large cohort of homosexual or bisexual men without laboratory evidence of HIV infection; in these cases disease is more indolent when compared to that observed in AIDS-KS
- review of cases reported to the CDC indicated that among HIV+ women, KS was four times more common in those who reported having sex with bisexual men than in those whose partners belonged to other HIV transmission groups

These clues have led many to suggest that AIDS-KS may be initiated by a sexually transmitted infectious agent other than HIV and that the severe presentation of KS in the HIV+ population merely reflects their compromised immune status. The recent decline in the proportion of AIDS cases presenting as KS may, therefore, be explained by the decline in the prevalence of an as yet unidentified sexually transmissible agent in the homosexual male population as a result of safe sex practices. While the role for cytomegalovirus (CMV), herpesvirus, human papillomavirus (HPV) and other viruses in the pathogenesis of KS has been suggested, there is currently little evidence supporting these theories. The most likely candidate is KSHV.

Using immunoblot assays for two latent nuclear antigens of KSHV, researchers recently reported that 32 (80%) of 40 patients with KS were seropositive for antibodies against KSHV, compared to 7 (18%) of 40 homosexual men without KS. Over a period of 13 to 103 months, 21 (52%) of 40 KS patients seroconverted 6 to 75 months before clinical manifestation of KS; median duration of antibody seropositivity with KSHV-associated latent antigens before diagnosis of KS was 33 months (Gao S-J, etal, NEJM, 25 July 1996, 335(4):233-241). These findings may also lead to development of a serologic test for KS based on the identification of KSHV. Also, if a virus is categorically associated as a cause of AIDS-KS, a vaccine may be developed to prevent this malignancy in HIV+ patients.

Investigators also detected KSHV in peripheral blood mononuclear cells (PBMC) of 24 (52%) out of 46 AIDS-KS patients but in none of 134 healthy blood donors or 26 controls. Presence of KSHV correlated with diminished immune response as indicated by reduced levels of CD4+ T cells. Moreover, presence of KSHV in PBMCs of HIV+ patients without KS was predictive of subsequent disease. Among 143 HIV+ patients without KS, followed for 30 months, 6 of 11 (54.5%) KSHV+ individuals went on to develop KS, compared to 12 out of 132 (0.9%) who were negative for KSHV. KSHV was rarely detected in sputum or throat swabs of HIV+ patients, explaining its limited spread (Whitby D, etal, The Lancet, 23 Sept 1995, 346:799-802).

In a study of the distribution of KSHV in tissues of healthy adults, researchers using polymerase chain reaction (PCR) identified sequences of KSHV in 22% of specimens from the glans or foreskin, 44% from prostate tissue and 91% from human semen of normal healthy males; in contrast, such sequences were present in only 5.5% of normal skin samples and in 7.1% of PBMCs. These findings may indicate that KSHV is a sexually transmitted disease (Monini P, etal, NEJM, 2 May 1996, 334(18):1168-1172).

Currently, there is no proof that KSHV is involved in the pathogenesis of KS; the virus may only be a passenger. If it is categorically demonstrated that KSHV causes KS, it will be one of the few instances of a viral cause for a human cancer. However, many questions still remain unanswered regarding the link of AIDS-KS and KSHV. For instance, if AIDS-KS is caused by a herpesvirus then antiherpes drugs administered to AIDS patients should decrease the incidence of KS within such groups. However, no such link was identified among 20,228 HIV+ individuals (5% of whom were diagnosed with KS, 91% of them homosexual men) studied in the Adult/Adolescent Spectrum of Disease (ASD) project. Antiviral drugs [acyclovir prescribed to 7,717 (38%) patients, ganciclovir to 1,475 (7%) and foscarnet to 320 (2%)] did not appear to confer any protection to those treated. Risk of KS was slightly increased with acyclovir and minimally affected by ganciclovir; only foscarnet appeared to reduce KS risk which may be attributed to its different mechanism of action (Jones JL, etal, Science, 24 Jan 1995, 267:1076-1078).

PATHOGENESIS

KS lesions originate in epithelial cells lining blood vessels. Under certain stimuli, these cells proliferate, causing the visible skin tumors associated with KS. At onset, epidemic KS is usually characterized by multifocal,

widespread lesions which may involve the skin, oral mucosa, lymph nodes, and visceral organs, such as the gastrointestinal (GI) tract, lung, liver and spleen. In some cases, KS involvement of lymph nodes or the GI tract may occasionally precede the appearance of cutaneous lesions. Most HIV+ individuals with mucocutaneous KS lesions feel healthy and are usually free of systemic symptoms as compared to HIV+ patients who first develop opportunistic infections. In an early report on the clinical manifestations of epidemic KS, among 49 patients, 8% had no skin involvement, 27% had localized or fewer than five skin lesions, and 63% had innumerable widely distributed skin lesions. At presentation, 61% of the patients had generalized lymphadenopathy and four of these patients who did not have skin lesions or detectable visceral organ involvement at the time of presentation were found to have biopsy-proven KS localized to the lymph nodes. In 45% of the patients studied, KS lesions were found in one or more sites along the GI tract.

Eventually, almost all patients with epidemic KS develop disseminated disease. Progression often proceeds in an orderly fashion from a few localized or widespread mucocutaneous lesions to more numerous and generalized skin disease with lymph node, GI tract disease and other organ involvement. Pleuropulmonary KS is an ominous complication usually occurring late in the course of the disease, especially in those patients whose death is directly attributed to KS. Otherwise, KS is rarely the cause of death; most patients with epidemic KS die of one or more complicating opportunistic infections.

KS may appear at any stage of HIV infection and, because those infected with HIV are now living longer, it is expected that KS may become more common. This increased risk with advanced disease may be related to the fact that as the immune system progressively declines over time, it releases various cytokines, including interleukin-1, interleukin-6, tumor necrosis factor, HIV Tat protein, and bFGF, that appear to accelerate KS growth.

DIAGNOSIS

AIDS-KS is histopathologically indistinguishable from all other types of KS. Visceral involvement in AIDS-KS is more common than in individuals not infected with HIV and may be asymptomatic. Diagnosis is made by visual inspection and confirmed by biopsy, although endoscopic biopsy may yield false-negative results if the tumor is in the submucosa.

CURRENT TREATMENT OPTIONS AND NOVEL APPROACHES

Few patients with AIDS-KS die as a direct result of this tumor. In approximately 70% of cases of AIDS-KS the primary goals of therapy are palliation of symptoms and cosmesis. Small, unsightly lesions are best treated with local therapy; often good cosmetic results are achieved by cryotherapy or intralesional vinblastine. These modalities are less effective in larger (>2 cm) or more nodular lesions, and are supplanted by irradiation. It is unlikely, however, that a complete response will be achieved with radiotherapy. Local treatment options include intralesional injections of interferon-α (IFN-α) or vinblastine, topical applications of liquid nitrogen, localized radiation therapy, retinoid gels, laser therapy, and photodynamic therapy. Patients who have widespread cutaneous KS but who are asymptomatic may derive cosmetic benefit from systemic therapy.

The 30% of cases presenting with visceral lesions are treated systemically with combination chemotherapy or systemic IFN-α. Obstructive lesions are effectively treated by laser ablation. It also appears that drugs that inhibit HIV protease, recently introduced into the market, may reverse KS lesions by increasing T-cell counts and reducing viral loads (Kraus P, Being Alive Newsletter, June 1996, p 3).

Treatment costs associated with KS are estimated between $5,902 for mild to moderate manifestations to $10,744 for severe disease, with a weighted average of $6,870 (Gable GB, etal, J AIDS and Human Retrovirology, 1996, 12(4):413-420). These costs are earmarked mostly for treatment of the disease.

Exhibit 3 lists drugs in development specifically for the treatment of AIDS-KS. Many other agents in early stages of development, targeting solid tumors, may also be potentially effective in the treatment of AIDS-KS.

Chemotherapy

Various chemotherapeutics, mostly in combination, are used in the treatment of advanced systemic AIDS-KS.

Combination chemotherapy for AIDS-KS that involves administration of three drugs, doxorubicin (Adriamycin; Pharmacia & Upjohn), bleomycin (Blenoxane; Bristol-Myers Squibb) and vincristine (Oncovin; Lilly) or VP16 (ABV regimen), is associated with a 70% response rate. However, toxicity associated with ABV therapy limits its utility as maintenance therapy. ABV is also contra-indicated during treatment for opportunistic infections.

Several new combination therapies that reduce toxicity are also under investigation. Bleomycin plus vincristine or etoposide (VP16) was shown to be an effective chemotherapeutic regimen for advanced AIDS-KS, with early addition of recombinant human granulocyte-colony stimulating factor (rhG-CSF) such as Amgen's (Thousand Oaks, CA) Neupogen, used to reduce incidence of treatment-induced neutropenia. A restrospective chart review was carried out in 19 AIDS patients with extensive, progressive mucocutaneous and/or visceral KS, treated with bleomycin (15 mg/m^2 IV) plus vincristine (2 mg IV) every two weeks, to evaluate the efficacy and toxicity of this chemotherapeutic regimen for the treatment of KS. Patients with peripheral neuropathy were switched from vincristine to intravenous VP16 (100 mg/mm^3). In addition, rhG-CSF (5 mcg/kg) delivered subcutaneously six days a week, was added upon availability.

Exhibit 3
Novel Drugs in Development for the Treatment of AIDS-Associated KS

Primary Developer/ Affiliate(s)	Generic Name/ Number/ Brand Name	Drug Type/Target/ Mechanism/Delivery	Status/Location/ Indication	Comments
Allergan Ligand Retinoid Therapeutics	9cRA/was LGD1057, now ALRT1057/ Panretin Oral	Chemically synthesized 9-cis retinoic acid/binds to both retinoic acid receptors (RARs) and retinoid "X" receptors (RXRs)/inhibits cell proliferation and induces apoptosis and cell differentiation/PO	Phase IIB/USA	See FO, pp 30, 31, 103, 250 and 255
Allergan Ligand Retinoid Therapeutics	9cRA/was LGD1057, now ALRT1057/ Panretin Topical	As above/topical	Phase III (8/96)	
Aronex/M. D. Anderson Cancer Center (licensor)/Genzyme	All-trans-retinoic acid, (ATRA)/AR-623/ TretinoinLF	Lipid-based, IV formulation of all-trans-retinoic acid	Phase II/III (9/95)/ USA	See FO, pp 211, 250 and 255
CarboMed/NCI	CM101 (GBS toxin)	Polysaccharide exotoxin produced by Group B Streptococcus	Phase I (completed 12/94)/USA	See FO, pp 58, 104, 194 and 196
Daiichi Pharmaceutical/ NCI	D-gluco-d-galactan sulfate/tecogalan sodium/DS-4152	Bacteria-derived sulfated polysaccharide/inhibits bFGF, VEGF, and a combination of bFGF and VEGF-stimulated proliferation, migration, and tube formation by choroidal endothelial cells *in vitro*; inhibits growth and chemotaxis of cells stimulated by bFGF and prevents binding of bFGF to cells at both its low and high affinity binding sites/IV	Phase I/USA	See FO, pp 195-196
EntreMed/Children's Hospital, Boston (developer), NCI; Bristol-Myers Squibb (ww licensee)	Thalidomide analogs	Antiangiogenic compounds/ blocks TNF-α	Phase II (4/96)/USA	See FO, pp 190, 195, 196, 269, 275 and 315
Genetronics		Electrically enhanced intratumoral delivery of bleomycin	Phase I/USA	See FO, p 269
Ilex Oncology	Piritrexim isethionate	Dihydrofolate reductase inhibitor; lipid soluble antifolate/enters cells by passive infusion; inhibits pyrimidine and purine nucleotides and DNA synthesis/IV, PO	Preclin/USA	The drug has been evaluated in patients with various solid and hematologic cancers
Imutec	Virulizin	Immunostimulant	Phase I/II (3/96)/ Canada	Clinical trials were restarted after they were suspended in July 1995; see FO, pp 60 and 155
Lidak Pharmaceuticals	N-docosanol/Lidakol	Topical	Phase II (b1/96)/USA	Bristol-Myers Squibb has commercial rights for oral herpes ww except in Japan
Ligand Pharmaceuticals	LGD1069/ Targretin Oral	Chemical retinoid/activates retinoid RXR receptors/PO	Phase IIB (8/96)	See FO, pp 105 and 251
Ligand Pharmaceuticals	LGD1069/ Targretin Topical	As above/topical	Phase I/IIA	

— *continued on next page*

Liposome Company/ U British Columbia, Canada; McGill U/Pfizer (ww licensee)	Doxorubicin/TLC D-99, TLC-DOX99	Liposomal formulation/IV	Phase II (4/95)/USA	See FO, pp 56 and 61
Milkhaus Laboratory/ New York Medical College	LDI-200	Chorionic gonadotropin formulation/mediates apoptosis	IND for Kaposi's sarcoma pending	See FO, pp 258, 269 and 274
NIH	Human chorionic gonadotropin (hCG)	Human chorionic gonadotropin/ inhibits 3H-thymidine incorporation in KSY-I cells; inhibits effects of human chorionic gonadotropin exhibited time and dose-dependence	Preclin/USA	Available for licensing: (301) 496-7735x270; also see Antakly T, etal, AACR96, Abs. 1543:226
NIH	IL13-PE38QQR	Chimeric molecule; IL-13 receptor-specific protein/ targets tumor cells	Research (8/96)/ USA	Available for licensing: (301) 496-7735 x284
Neopharm	Doxorubicin/LED	Liposomal formulation of doxorubicin	Phase I/II/USA	
Norris Comprehensive Cancer Center, USC School of Medicine		Snake venom distintegrin/binds RGD-dependent integrins on cell surface (RGD peptides bind to integrins on tumor cell surface and inhibit tumor cell binding to the extracellular matrix)	Preclin/USA	Fry B, etal, AACR96, Abs 3356:492
PDT/Pharmacia & Upjohn (licensee)	Tin ethyletiopurpuria (SnET2)	Photodynamic therapy/ nonthermal light activates SnET2 to produce free oxygen radicals	Phase III (b3/96)/USA	See FO, p 64
Pharmacyclics/ Hoechst Celanese	Lutetium-texaphyrin/ Lu-Tex	Texaphyrin-based photosensitizer activated by red light (720-760 nanometers) to generate cytotoxic singlet oxygen molecules	Phase I (9/96)/USA	See FO, p 239
QLT Phototherapeutics (was Quadra Logic Technologies)/Ligand (Canada); Sanofi Winthrop (USA); Lederle Japan (American Home Products and Takeda jv; marketing, Japan)	Porfimer sodium; dihematoporphyrin ether/CL-184116/ Photofrin	Photodynamic therapy	Phase I/USA	Approved for other indications worldwide; see FO, pp 29, 56, 101, 271 and 272
Repligen Clinical Partners/New York U	Recombinant platelet factor 4 (rPF4)	Recombinant protein/IV SC and intralesional	Phase II/USA	Repligen terminated its development and marketing agreement with Repligen Clinical Partners in April 1996; rPF4 is available for licensing
Seragen	IL-6 fusion protein/ DAB_{389}IL-6	Binds to IL-6 receptors; targets and kills tumor cells expressing IL-6 receptors	Preclin (3/96)/USA	See FO, pp 245-246 and 260
Sheffield Medical Technologies/Beth Israel Hospital	SCAL-1	Topical	Clinical (4/95)/USA	See FO, pp 102 and 195
Sugen/NCI (CRADA)	SU101	Platelet derived growth factor (PDGF) antagonist/inhibits PDGF TK-mediated cell signalling/oral	Phase I (96)/USA/	
Takeda/Takeda Abbott Pharmaceuticals (TAP)	TNP-470 (AGM-1470)	Synthetic analog of the antibiotic fumagillin/ antiangiogenic agent/ inhibits neovascularization/IV	Phase II (3/95)/USA	Phase I (ASCO, May 1995, Abs # 794); see FO, p 195

Four patients were previously treated by radiotherapy, two with INF-α and two with chemotherapy. Among 15 evaluable patients to date, overall objective response rate was 100%, with four CRs (27%) and 11 PRs (73%). Time to CR was 12 weeks and PR eight weeks while duration of response was 10 weeks and seven weeks, respectively. Three of six patients treated with rhG-CSF, and all nine patients who did not receive the drug, developed neutropenia (Routy JP, etal, Abstracts of the XI International Conference on AIDS, Vol 1, p 97:MoB1249).

Another combination regimen consisting of doxorubicin, bleomycin and vinblastine (Velban; Lilly), administered together with rhG-CSF, was also active and fairly well tolerated for the treatment of aggressive AIDS-KS, although response to this regimen was not sustained after therapy was stopped. Nine HIV+ patients with biopsy-proven KS received six cycles (one every 21 days) of chemotherapy with intravenous doxorubicin (40 mg/m^2) and vinblastine (6 mg/m^2) on day one and bleomycin (15 U) on days one and 15. In the case of disease progression after a primary response, patients were randomly assigned to the combination regimen or to etoposide (150 mg/m^2) three days per month. Every other day, rhG-CSF was administered from the third to the 14th day of each cycle. Records of 13 HIV+ patients diagnosed with "poor risk" KS in 1991-1992, who had not been treated with chemotherapy, substituted as controls. There were six PRs (66.6%) of median duration of 12 weeks and disease stabilized in two patients. Seven patients died within an average follow-up of 15 months; probability of survival at 12 months was 53% among those treated compared to 15% in the control group (Del Bianco R, etal, Abstracts of the XI International Conference on AIDs, Vol 2; p 97:WeB3238).

Liposomal doxorubicin, Doxil (was DOX-SL), supplied by Sequus Pharmaceuticals (Menlo Park, CA), was recently approved for the treatment of AIDS-KS for patients who either failed or are intolerant of standard combination chemotherapy. Doxil is a formulation of doxorubicin hydrochloride encapsulated in long-circulating pegylated Stealth liposomes, that extends the half-life of circulating drug from 10 minutes for free doxorubicin to 50 hours. Doxil was approved in the USA in November 1995 and launched a month later as second-line treatment of AIDS-KS. Accelerated approval for Doxil had been recommended in February 1995. The drug was approved for a shelf-life of 20 months. In July 1996, Doxil was also approved in the 15 member nations of the European Union (EU) where it will be marketed under the trade name Caelyx. In October 1996 Sequus awarded exclusive worldwide marketing rights of Caelyx to Schering-Plough, except for the USA, Japan and certain small markets subject to prior distribution arrangements. Under the terms of the multi-year agreement, Schering-Plough will make an upfront payment of $5.3 million and will potentially pay Sequus up to $27 million, provided certain targets are met. Schering-Plough will purchase the drug from Sequus and also fund a portion of the drug's ongoing clinical development for the treatment of various solid tumors.

Doxil is administered intravenously (20 mg/m^2) for 30 minutes, once every three weeks. In the USA, Doxil is priced at $1,200 per course. In the first half of 1996, Sequus reported Doxil sales of approximately $8.7 million. Doxil is manufactured by Ben Venue (Bedford, OH). Sequus is marketing Doxil in the USA using a direct sales force. Sequus is committed to conduct a phase IV (post-marketing) clinical trial to evaluate the performance of Doxil in the clinical setting.

Doxil was approved as second-line therapy for AIDS-KS based on results from a clinical trial involving 77 AIDS patients who failed standard chemotherapy. In this population, Doxil elicited a 27-48% response rate with mean duration of response lasting 73 days. In patients previously treated with doxorubicin, partial responses were observed in 30% of patients with a median response duration of 89 days.

Doxil is also being studied as first-line treatment for AIDS/HIV-KS. Two phase III trials were conducted comparing Doxil with ABV and BV regimens as first-line treatment for AIDS-KS. Doxil demonstrated promise as first-line treatment in a prospective multicenter phase III clinical trial of 239 patients with AIDS-KS randomized to Doxil (118 patients at a dose of 20 mg/m^2) or ABV (110 patients). Patients were treated a mean number of 5.1 cycles with Doxil and 3.8 cycles with ABV. There were 51 (43.2%) PRs among those treated with Doxil and disease stabilized in 66 patients (55.9%) compared to 24.5% and 67.3%, respectively, among those treated by ABV (Northfelt DW, Blood, Suppl 1, 15 Nov 95, 86 (10), p 382a, Abs. 1515).

Doxil also demonstrated a higher response rate than the BV regimen. A total of 241 patients with advanced AIDS-KS were randomly assigned to Doxil (20 mg/m^2) or bleomycin (15 mg/m^2) and vincristine (2 mg). Both groups were well matched for prognostic factors. The overall response rate in the 116 evaluable Doxil-treated patients (out of 121 patients) was 58.7%, with seven CRs (5.8%) and 64 PRs (52.9%). In contrast, the response rate in the 102 evaluable patients treated with BV was 23.3%, with one CR (0.8%) and 27 PRs (22.5%). Mean time to response was more rapid in the Doxil group (48.8 days) compared to the BV group (61.4 days). Generally, Doxil was better tolerated but proved to be more myelosuppressive (Stewart S, etal, Program Supplement of the XI International Conference on AIDS, p 27:LBB6026).

Liposomal daunorubicin, marketed as DaunoXome by NeXstar Pharmaceuticals (Boulder, CO), was deemed approvable by the FDA as first-line therapy in advanced AIDS-KS in July 1995, one month after it was recommended for approval by the Oncological Advisory Committee of the FDA. The drug was subsequently approved in April 1996 when it was also launched in the USA market.

It was also approved in Canada in April 1996. In Europe, DaunoXome has been approved in 12 EU countries. In Sweden, DaunoXome is marketed by Swedish Orphan (Vallentuna, Sweden). The drug is also under development for breast cancer, small cell lung cancer and hematologic malignancies.

In a pivotal phase III randomized 13-center clinical trial that enrolled 227 men in their mid-thirties with advanced AIDS-KS, treatment with DaunoXome (40 mg/m^2 every two weeks) was compared with ABV. DaunoXome proved comparable in efficacy (survival, time to treatment failure and response rate) to ABV but was associated with a lower incidence of such side effects as neuropathy and alopecia. Quality-of-life considerations also favored the DaunoXome regimen. A higher dose of DaunoXome (60 mg/m^2 every two weeks) was also tried as second-line therapy in 80 patients who progressed on ABV or DaunoXome (40 mg/m^2). Clinical benefit was observed in 34 patients (eight experienced a PR and 24 had stable disease), and no response in 34 (27 progressed and 7 died).

Topical retinoid gel, Targretin Topical, in development by Ligand Pharmaceuticals (San Diego, CA), also appears to efficacious in the treatment of cutaneous AIDS-KS lesions, but is accompanied by cutaneous irritation and requires multiple applications. Fifty-nine HIV+ patients with biopsy-proven KS were randomized to either 0.5% or 1.0% Targretin twice daily, increasing to 1.0% gel four times daily or the maximum dose tolerated. If necessary, the dose was dropped to 0.1% gel for patients who experienced drug-related adverse effects. Each patient's lesions were divided into control and treated lesions and evaluated every two weeks for 16 weeks and every four weeks thereafter. Among 46 evaluable patients, there were seven PRs (15.2%) with three PRs occurring at the 1.0% four-times-daily regimen. Median duration of response was 18 weeks. Eleven of 33 patients on the 0.5% gel regimen experienced such treatment-related adverse effects as rash, exfoliative dermatitis, eczema, or pain; twelve of 45 patients on 1.0% gel suffered from comparable side effects (Lesung GS, etal, Abstracts of the XI International Conference on AIDS, Vol 2, p 98:WeB 3241).

All-trans-retinoic acid (ATRA) administered orally to AIDS patients with low-risk KS was well tolerated and very helpful in controlling the disease. In a prospective, open-label, non-randomized study, 20 male HIV+ patients with CD4 counts of <200 cells/mm^3 and low-risk KS with at least four measurable KS lesions, were treated with oral ATRA (45 mg/m^2 daily) for three months. Antiretrovirals were allowed if initiated more than four months prior to inclusion in the study. Response was observed after at least eight weeks in most of those treated, consisting of flattening and clearing of lesions. At day 90 of treatment, there were eight PRs (40%), disease stabilized in eight patients (40%) and progressed in four (20%). Further improvement was observed in six patients with PRs who continued on ATRA. The most frequent drug-related adverse effects were chelitis (95%), transient headaches (60%), hypertriglyceridemia (60%), and skin dryness (45%). No patient discontinued therapy because of side effects. The fact that ATRA in no way affects HIV status *in vivo* suggests that it may be safely administered to HIV+ patients (Saiag P, etal, Abstracts of the XI International Conference on AIDS, Vol 1, p 303:TuB2220).

Paclitaxel (Taxol; Bristol-Myers Squibb) is also being investigated in AIDS-KS. In an NCI-sponsored clinical trial involving severely immunocompromised HIV+ patients with advanced, poor prognosis KS, treatment with Taxol elicited PRs in 13 out of 20 evaluable patients, disease stabilized in six and progressed in one. Taxol (135 mg/m^2) was administered intravenously over three hours, every 21 days. Neutropenia, the most frequent dose-limiting toxicity, usually resolved between cycles of therapy. Other unexpected adverse effects seen included late fevers, rash, rise in creatinine (2 patients), cardiomyopathy (one patient), and eosinophilia (Savill MW, etal, The Lancet, 1 July 95, 346:26-28). A paclitaxel regimen of 100 mg/m^2 administered intravenously over 3 hours, every two weeks, was also effective, resulting in 16 PRs (53%) among 30 evaluable patients with relapsed or refractory advanced AIDS-KS; disease stabilized in the remaining 14 patients (Gill PS, etal, ASCO96, Abs. 854). A low-dose paclitaxel regimen (30mg/m^2), administered intravenously by a 3-hour infusion for four weeks, followed by one-week rest, was also active in advanced AIDS-KS (Mega A, etal, ASCO96, Abs. 859). Several other phase I trials with paclitaxel in KS are ongoing (see FO, V1 #7/8, p 185).

Radiation Therapy

Radiotherapy is an effective and well tolerated approach for the treatment of HIV+ individuals with localized AID-KS. A single fraction of 8 Gy results in a response rate and cosmesis equivalent to higher doses or more fractionated regimens. To determine the optimal radiotherapy protocol for response and surrounding normal tissue cosmesis in the treatment of localized KS, 57 HIV+ patients with 596 cutaneous KS lesions were treated with either radiotherapy using 16 Gy in four fractions over four days or radiotherapy using 8 Gy in a single fraction. One hundred seventy lesions were randomized in the study, with the remainder being treated according to the patients' preference.

The overall response rate was 80.9% (482/596). Lesions treated with 16 Gy in four fractions had a response rate of 87.8% (174/198) while the single fraction treatment response rate was 77.4% (309/398). There was no statistical difference between the two groups. Response duration for both regimens was 19 weeks. Cosmesis of an acceptable quality was reported in 91.9%

(366/398) of lesions treated with the single fraction and 85.8% (170/198) with the fractionated regimen (Harrison M, etal, Abstracts of the XI International Conference on AIDS, Vol 1, p 98:MoB1253).

Photodynamic Therapy

Most photodynamic therapies in development may prove effective in the management of cutaneous AIDS-KS.

Delta-aminolaevulinic acid (5-ALA), used as a photosensitizer in photodynamic therapy, is an effective palliative treatment of AIDS-KS. In a pilot study, four HIV+ individuals (CD4 counts between 2 to 370 cells/mm^3) with seven KS lesions were treated topically with an ointment containing 20% 5-ALA; the lesions were then covered with Tegaderm. After six hours of occlusion, treated sites were irradiated using a 600 to 730 mm red light (90 to 120 mW/cm^2); exposure of six to twenty minutes resulted in a total dose of 100 to 150 J/cm^2. Local anesthesia was unnecessary. All lesions responded to photodynamic therapy after a single treatment, with one CR and six PRs. Additional patients are being recruited to determine the value of this approach in controlling AIDS-KS (Schöfer H, etal, Abstracts of the XI International Conference on AIDS, Vol 1, p 98:MoB1251).

Tin ethyletiopurpuria (SnET2), a photosensitizer under development by PDT (Santa Barbara, CA) in collaboration with Pharmacia & Upjohn, is in phase III trials for various cutaneous malignancies, including AIDS-KS lesions in advanced disease (also see FO, V1 #2/3, p 64). In a phase I/II clinical trial, 11 AIDS patients with 91 KS lesions were treated according to a drug escalation protocol. At each drug level, lesions were irradiated with 664 ± 7 nm light at 100, 150, and 200 J/cm^2, 24 to 72 hours after the SnET2 infusion. One lesion was treated in each of nineteen patients by exposure to 0, 200 J/cm^2 and 300 J/cm^2, 24 hours after infusion with SnET2 (1.2 mg/kg). Responses were determined by objective, bidimensional measurements of lesions. At 1.2 mg/kg of SnET2, the objective response rate (CR + PR) was 78%. In a phase I clinical trial, threshold drug dose required for clinical tumor response was found to be greater than 0.8 mg/kg. Lower drug doses did not elicit an objective response regardless of the light dose. The overall response rate for macular stage KS lesions was 34% (22 % CR, 12% PR) and 84% for papular stage (32% CR, 53% PR). CR rates were higher (36%) for lesions treated at 300 J/cm^2, compared to those treated at 200 J/cm^2 (28%) (Grekin RC, etal, Abstracts of the XI International Conference on AIDS, Vol 2, p 98:WeB3243).

Antiretroviral Therapy

The first case of resolution of AIDS-KS occurred in a 32-year-old HIV+ male who was being treated with saquinavir (Invirase; Hoffmann-La Roche). In early September 1995, while on antiretroviral therapy consisting of was zidovudine (ZDV or AZT; Glaxo Wellcome) and lamivudine (3TC; Biochem Pharmaceutical), this patient (CD4 count of $40x10^9/mm^3$) developed biopsy-proven KS. Twelve cutaneous lesions appeared over the next three months but no visceral KS was detected and no specific KS chemotherapy was initiated. Despite a switch to a combination therapy consisting of 3TC and stavudine (d4T, Zerit; Bristol-Myers Squibb), new lesions persisted and the CD4 count continued to decline. Saquinavir (1800 mg daily) was added on December 1, 1995 when the CD4 count was at $30x10^9/mm^3$. By January 15, 1996, the CD4 count rose to $100x10^9/mm^3$ and after seven weeks of saquinavir therapy, ten KS lesions completely disappeared and the two remaining lesions lost all nodularity and were reduced to 10% of original size (Workman C, etal, Abstracts of the XI International Conference on AIDS, Vol 1, p 303:TuB2217). Clinical results are probably attributed to restoration of immune function as measured by CD4 count rather than any antineoplastic activity of saquinavir.

Hormonal Therapy

Hormonal control of KS is the focus of research at the Institute of Human Virology located at the University of Maryland (Baltimore, MD) founded by Robert Gallo, MD. Findings that a pregnancy hormone, the β-chain of human chorionic gonadotropin (hCG), kills cells of the KS Y-1 cell line (Lunardi-Iskandar Y, etal, JNCI, 5 July 1995, 87(13):974-981) that was shown to induce malignant metastatic tumors in nude mice (Lunardi-Iskandar Y, etal, Nature, 4 May 1995, 375:64-68), presumably by apoptosis, lead to various clinical trials of hCG in AIDS-KS.

Human chorionic gonadotropin (Pregnyl; Organon), administered by local injection, induced a significant reduction in KS tumor size in about two-thirds of AIDS patients treated. In a multicenter trial, 12 AIDS patients (median CD4 cell count of 50 cells/mm^3) received intralesional injections of 500 IU of hCG in four index lesions once a week for two weeks, followed by 2500 IU of hCG subcutaneously five days a week for six additional weeks. Eight of those treated had a prior history of opportunistic infections at baseline and nine were previously treated by chemotherapy for KS. Eight of 11 (72.7%) evaluable patients showed a significant decrease in tumor area of the index lesions ranging from 10% to 40% from baseline values, with lesions becoming paler and more flattened. However, new lesions appeared in four of the eight responders. One patient with pulmonary KS had a dramatic improvement and two patients are still on hCG therapy a year after study enrollment. Three patients failed to respond. Tolerance was excellent (some local pain at site of intralesional injection in four individuals), and there was an increased appetite associated with hCG use in six patients, with attendant weight gain (Picard O, etal, Abstracts of the XI International Conference on AIDS, Vol 1, p304:TuB2227).

Cytokine Modulation

The putative role of various cytokines in the development of AIDS-KS has spurred investigation of various modulators of cytokine release, including soluble receptors, neutralizing antibodies, oligonucleotide-based drugs, inhibitory cytokines (IL-4, IFN-α) and antiangiogenesis agents, among others. Both IFN-α 2b (Intron A; Schering-Plough) and IFN-α 2a (Roferon; Hoffmann-La Roche) have been approved for the treatment of KS. Vesnarinone (Arkin; Otsuka), a drug sold in Japan as a cardiostimulant and an inhibitor of TNF and IL-6, is also being investigated in the treatment of AIDS-KS (Jamie Von Roenn, MD, Northwestern University School of Medicine, Chicago, IL).

ISSUES IN ONCOLOGY

RANDOMIZED CLINICAL TRIALS IN ONCOLOGY

Randomized clinical trials (RCTs) are comparative studies that use the principle of random allocation to determine the most appropriate intervention option for a specific condition. RCTs establish the relative efficacy of medical interventions in relation to various comparators (no intervention, placebo, standard practice, or a combination thereof). RCTs represent the most rigorous and extensive type of scientific inquiry of a new treatment (Pocock SJ, Clinical Trials: A Practical Approach, John Wiley and Sons Ltd, 1983). The strength of RTCs over other methodologies relies on minimizing influence of extraneous effects across comparison arms, which is attained through appropriately conducted randomization. Balancing factors (across study groups) which may influence the outcome of the comparison, permits the unequivocal determination that the best choice among the interventions being compared is the one associated with the greater observed benefit. RCTs have been widely used to evaluate efficacy of clinical therapy for the last 40 years.

Although there is no current substitute for a randomized design, RCTs need to be longer, more practical and appealing to participants, providers and funders, and more informative about implications of new and old technologies. This article addresses use of RCTs to assess interventions associated with the management of cancer and incorporates information presented at a special session on RCTs during the 1996 ASCO meeting. Unless stated otherwise, RCTs refer to the phase III clinical trial model. RCTs, however, may also be the design of choice of phase I and phase II studies.

WHAT ARE ONCOLOGY RCTS?

Oncology RCTs are planned clinical trials designed to determine the most appropriate option(s) for the management (screening, diagnosis, chemoprevention, therapy and palliation) of cancer and to define the role played by environmental risk factors or genetic predisposition in the incidence and type of malignancy (see Exhibit 4). Because cancer encompasses a broad group of disease states with complex clinical course, different diagnostic and therapeutic requirements and dissimilar prognoses, RCTs in cancer need to be highly specific.

Use of RCTs in oncology is a rather recent trend. During the past five decades, the treatment of cancer evolved from mainly a surgical intervention into a complex array of primary drug and supportive therapies and palliative modalities. Of course, surgery still plays a pivotal role as a curative treatment for certain cancers, in tumor debulking for others and as a palliative approach in advanced disease. Also, in spite of intensive R&D during this period, alternative cancer therapies increased the cure rate of major cancers by only 5% to 13%; striking progress was made in finding cures only for some relatively rare cancers (e.g., acute lymphocytic leukemia, Hodgkin's disease, testicular cancer, choreocarcinoma, etc.).

Currently, RCTs are used extensively in oncology to show efficacy of novel treatment approaches as compared to standard therapies, and their role will continue in the immediate future because the etiology of most cancers has not been elucidated to permit selection of an intervention that specifically targets that cause. No agent has been identified to date that actually cures most cancers. In most situations, investigators test various agents against each other in selected populations to determine which results in the most desirable endpoints such as tumor shrinkage, increased disease-free and overall survival, and better quality of life (QOL). In these comparisons, RCTs are the most reliable approach to arriving at clinically useful treatment options.

RCT results may also be used in deciding appropriate treatment options in the clinical setting. As more and more agents enter the clinic, RCT findings will become increasingly more crucial in helping the oncologist choose treatment for individual patients. Therefore, properly conducted RCTs, combining as broad a patient population as possible, may become effective marketing tools in the commercialization of new agents. To date, RCTs have been instrumental in enabling off-label use of approved drugs. As more antineoplastic agents become commercialized for specific cancers, off-label use will compete with approved alternatives for a given indication, further expanding physician options and making treatment selection increasingly more challenging.

In the future, RCTs are expected to become more complex and more difficult to perform as the number of agents to be evaluated grows exponentially. Patient recruitment will also become more challenging as drugs under evaluation may provide only marginal benefit when compared head on with existing therapies. In order for a patient to be a candidate for an RCT, it must be shown that the agent under evaluation is expected to offer a significant advantage over standard therapy.

However, not all evaluations of oncology treatments need rely on RCTs to demonstrate efficacy. For instance, as more and more is learned about the mechanisms of malignancy at the molecular level, it may be sufficient in a clinical trial to demonstrate that the target was addressed by the treatment. For instance, in the case of genetic therapy, successful replacement of a mutant gene with its wild counterpart may be sufficient to show that the intervention was effective. In such a case, the endpoint may be proof of expression of the wild gene irrespective of its effect on the malignancy. If the intervention is successful but has no universal effect on the cancer, then the treatment would be considered as having failed.

RCT PATIENT SELECTION AND RANDOMIZATION APPROACHES

There are two basic issues in the design of RCTs in terms of populations to be evaluated:

- patient selection criteria (although RCTs are simpler to perform in highly selected and homogeneous populations, restrictive enrollment approaches may compromise their utility as treatment guidelines in the clinical setting; see Exhibit 5)
- proper randomization in terms of statistically adequate populations and fully delineated randomization variables

Patient Selection

Although group homogeneity through refined admission criteria has no effect on the comparison itself, patient selection is a major influence on the interpretation of trial findings (Buyse ME, Cancer Sur 8 (1): 100-5; 1989). Assembling a group with similar epidemiological and demographic characteristics (e.g., age, socioeconomic status, ethnicity, treatment compliance, etc.) probably increases patient adherence to trial protocols and maximizes information yield. Therefore, the goals of randomizing and qualifying participation are different in the sense that, while randomization ensures the comparability of the groups in relation to the intervention, selection allows interpretation of results as suitable to those characteristics defined in the enrollment criteria. What drives the selection process is a need to assure that the intervention effect can be replicated in similar scenarios.

Use of well-defined populations is of particular importance in oncology RCTs. Inappropriate patient selection may mar interpretation of study results and raise questions about the study's credibility and the actual degree of an observed benefit. However, it is not clear how much RCT results influence decisions in the clinical setting where it is often unlikely that the patient under treatment meets all the criteria of the original study enrollees. Even patients who would not have been eligible for the RCT are usually treated in a life threatening situation. Generalized off-label use of oncology drugs points to this dilemma.

After establishing RCT entry criteria, such as disease stage, it is common that enrollees are selected from eligible pools that are healthier and more motivated than their cohorts, so that those chosen do not mirror the cohort at large based on most variables with the exception of disease stage. As the composition of this RCT group becomes increasingly homogeneous it further departs from resembling the population at large. For instance, RCTs have difficulty recruiting non-whites, patients from certain ethnic groups and those in poor health or of lower socioeconomic status. This phenomenon makes RCT results difficult to reproduce in a real world setting. This is particularly problematic in RCTs performed in countries such as the USA where populations are racially, ethnically and economically diverse.

Although RCTs are usually designed to establish effectiveness and safety and, therefore, need not address other issues arising from patient selection, nevertheless issues such as setting and sample size often render RCT conclusions difficult to extrapolate. The goal of RCTs is to establish if the intervention is effective on average for a selected group of patients who comply with treatment guidelines. However, because of patient selection, RCTs do not provide information regarding outcome of such intervention in patients who are not eligible, not selected, decide not to participate or are not retained in RCTs. Therefore, results of such RCTs are not readily applicable to the average cancer patient at large.

RCT population recruitment is influenced, with various levels of intensity, by referral practices, technology, protocol, participant profile, health status, treatment history and other factors which are particular to each trial setting. Also, populations may become further selected by unforeseen events after the RCT is initiated, such as individual patient decision not to remain in the RCT, unexpected deaths from other causes, or severe reaction to treatment/toxicity. In such situations, results are reported based on "evaluable" patients, further compromising translation of results to the clinical setting.

Statistical Considerations

An important consideration in RCT design is accrual of an adequate population size to permit demonstration of an intervention effect and prevent the likelihood of observing a benefit by chance alone. Because stricter selection criteria are usually required in secondary and tertiary RCTs for cancer interventions, they result in small sample sizes and less convincing results. Sample size remains an issue in oncology RCTs with several barriers to patient participation, such as:

- unwillingness of patients to undergo randomization
- short life expectancy
- ineligibility because of specific disease staging requirements

Exhibit 4
Randomized Clinical Trials in Oncology

Intervention	Size (# of patients)/ Duration	Purpose and Comparators	Surrogates and Endpoints	Comments
Primary Prevention – Prevention of cancer in high-risk healthy and newly diagnosed populations				
Screening (genetic, dietary, environmental factors)	10,000 to 100,000/years to decades	Screening versus non-screening	Cancer incidence, markers, behavioral changes, QOL	Psychosocial, insurance and job implications may arise, especially with genetic testing
Diagnostic (pre-malignancies and primary tumors)	1,000 to 100,000/years to decades	Diagnosis versus non-diagnosis	Markers, pre-cancer and cancer incidence, mortality	Feasibility of diagnostic trials is diminished by the prevalence of the procedure
Chemoprevention and Treatment	100 to 100,000/years	Multiple agents and doses, usually via factorial designs	Incidence and prevalence of pre-malignant conditions, markers, progression-free intervals, QOL, disease-free survival, mortality	Agents may provide multiple levels of protection; compliance, toxicity and costs are major issues; small reductions in incidence represent major population impact
Secondary Prevention – Early detection of cancer and therapeutic intervention				
Diagnostic (secondary tumor, monitor response)	<100 to low 1,000s/ months to years	New approach versus established diagnostic method	Diagnostic delay, accuracy, time to recurrence, response to primary treatment, markers, time to progression, mortality	Common issues include cost effectiveness; participant selection through screening, compared to presentation or referral; difficulty in evaluating standard care technologies; difficulty in interpretating small trials, sub-group analysis, and RCTs with restrictive enrollment criteria; multiple economic disincentives to RCTs; lack of assessment of trade-off between validity, reliability and cost
Therapeutic (chemotherapy, radiotherapy, surgery)	Low 100s to 1,000s/ months to years	Single or multiple treatment combinations versus standard therapy	Response to primary treatment, markers, toxicity, time to recurrence, progression-free intervals, QOL, disease-free survival, mortality	
Adjuvant therapy	100s to low 1,000s/ months to years	Combination with standard therapy versus standard therapy alone	Markers, toxicity, time to recurrence, progression-free intervals, QOL, disease-free survival, mortality	
Tertiary Prevention – Patients with disseminated disease				
Palliative chemotherapy, transplants, neo-adjuvant therapy, supportive care	<100 to >1,000/ weeks to months	Therapeutic combinations, symptom control, side effects, higher doses versus standard care	QOL (toxicity, major surgery, limb/organ conservation), mortality	Neo-adjuvant interventions currently used with surgery and organ-sparing therapy; supportive care trials are infrequent because of difficulty in recruiting patients

THE IMPACT OF RCTS IN ONCOLOGY

Findings from RCTs have greatly contributed to an increased understanding of the pathobiology of neoplasia and are responsible for most of the major clinical advances in cancer treatment. In the future, RCTs are expected to play an increasingly important role in oncology by:

- establishing effectiveness and other important attributes of certain drugs/therapies as compared to competitive approaches; RCTs may represent the best tool available to investigators to assess existing approaches in the management of cancer in terms of effectiveness, safety, side effects impacting QOL and even costs
- establishing effectiveness of certain chemoprevention approaches as compared to no therapy or placebo
- identifying risks of certain behaviors/exposures that may lead to carcinogenesis
- assessing the impact of diagnostic and screening techniques in early detection/prevention of cancer

Particularly in oncology, RCT findings also serve as treatment guidelines for physicians who must choose the most appropriate treatment for their patients among,

possibly, a variety of options. Usually, treatment guidelines, drug labeling (recommended dosage, toxicity profile, exclusions) and phase IV protocols are based on results of phase III RCTs. Well-conducted RCTs allow physicians to treat patients using new drugs with some degree of confidence of their superiority over standard therapy.

Use of RCTs in Oncology is Expected to Intensify

The oncology field is currently experiencing a profound change. Frustrated after many years of perceived increases of R&D spending with marginal results, the public is demanding more effective interventions aimed at earlier disease stage and alternative approaches to current norms, such as more aggressive treatments and improved palliative care. At the same time, health care systems around the world continue to realign their priorities to maximize their return from health care expenditures and R&D investments.

Amidst these trends, new drugs are being approved at an accelerated pace for the treatment of major cancers. In some cases these new drug therapies represent the first competitive approach to be approved in decades. For instance, irinotecan, recently approved in the USA, is the first drug in 40 years to be commercialized for the treatment of advanced colorectal cancer. Expected accelerated approvals of oncology-related therapeutics, already evident by the launch of several new drugs, will make it increasingly difficult for the oncologist to choose appropriate treatment without adequate comparative information. Accelerated FDA approval is already evident. Until recently, in order to approve an antineoplastic, the FDA required developers to provide evidence of improved survival and quality of life (QOL). However, in 1996 the FDA revised its stance by announcing that it will adopt other endpoints such as response rates (i.e., an early indicator of drug activity). To ensure that positive RCT findings for the newly approved agents are replicated in the clinical setting, developers are being asked to support pre-approval findings with survival and QOL data obtained via post-approval phase IV clinical trials.

RCTs may also benefit from possible coverage of Medicare beneficiaries who participate in such trials. A newly introduced bill (S. 1963, the Medicare Cancer Clinical Trial Program Coverage Act of 1996) would require that Medicare embark on a five-year demonstration project to reimburse Medicare enrollees participating in clinical trials at the same level as those treated by standard therapy. Even if the bill does not pass immediately, this development is expected to increase participation of older Americans in RCTs in the long run.

TYPES OF RCTS IN ONCOLOGY

Oncology RCTs may be classified according to current or future cancer interventions addressing induction and pre-malignant, primary, local invasive and metastatic disease (see Exhibit 4). Assessment of primary prevention focuses on the interruption or prevention of premalignant lesions (Alberts DS and Garcia DJ, J Nutr 125 (3 Suppl): 692S-697S; Mar 1995) while secondary prevention relates to blocking or reversing progression to invasive disease. RCTs in tertiary cancer prevention evaluate reduction of disability in advanced stages of malignancy. RCTs that evaluate chemotherapeutic agents as first-line therapy for primary tumors may be considered part of tertiary prevention strategies because, to date, these agents have only resulted in QOL improvements, rather than better treatment response or increased survival (Frei E III, Cancer 74 (9 Supplement): 2610-3; Nov 1, 1994).

RCTs may also play a role in identifying the role of interaction of genetic and environmental factors in the development of cancer. In this case, randomization among those tested and those who decline testing may provide information as to the value of testing and its effects on various endpoints, addressing not only physical health but also psychosocial issues.

RCTs in Cancer Prevention

Although RCTs are the most effective means of evaluating methodologies to prevent disease in high risk individuals, they are particularly challenging to perform and fund. Because they involve patients without a specific diagnosis, seen on an outpatient basis, such RCTs do not fit into the traditional mold and may not be reimbursable. Also, in order to evaluate the effect of an intervention in disease prophylaxis, RCTs must enroll large populations that are followed for long periods of time. Population selection often requires extensive screening of all potential enrollees for the occasional participant, further increasing study costs (Fleming ID, Cancer Suppl, Nov 1, 1994, Vol. 74, No. 9). As a result, RCTs to evaluate cancer prevention interventions are very expensive to perform and, therefore, few have been attempted in cancer.

Few trials have been undertaken to assess the impact of putative cancer prevention strategies, and most of them have been supported by public funds. Also, results from such trials often introduce more questions than answer them, necessitating additional investigation. For instance, a trial involving 29,133 male smokers, undertaken to establish the benefits of intake of vitamin E, or beta-carotene, or both, in preventing cancer, actually showed that beta-carotene increased the incidence of lung cancer. Because it takes years to obtain relevant information from these trials, their benefits are dubious. Also, as populations participating in these trials are observed over long periods of time, early results are often altered by later findings. Such was the case with tamoxifen (Nolvadex; Zeneca) under investigation as a chemoprevention strategy in women at high risk for breast cancer. Although the risk to benefit ratio still favors tamoxifen as a long-term chemoprevention strategy in breast cancer, possiblity of serious side effects has dampened enthousiasm regarding its benefits.

RCTs to Evaluate Screening and Diagnostic Approaches

The purpose of RCTs in cancer screening and diagnosis such as *in vitro* detection of biochemical markers and *in vivo* imaging and endoscopic procedures is to obtain a better understanding of the value of these procedures in the early detection and subsequent staging, monitoring and prognosis of cancer. Also, diagnostic and screening RCTs are needed to support development and validation of carcinogenic markers that are used to identify at-risk subjects who may benefit from chemoprevention as well as guide therapy. In the case of cancer screening, RCTs may be used to:

- evaluate the impact of early detection in treatment outcome
- assess the cost effectiveness of screening programs
- determine the overall impact of the screening program on certain endpoints (response, overall and disease-free survival, toxicity and other side effects, functional status and QOL, symptom reduction, etc.)

Role of RCTs in Evaluating Treatment Modalities

RCTs in primary therapies are used to evaluate new drugs, novel drug combinations, new treatment modalities and technological advances affecting established modalities (Kaufman D, CA Cancer J Clin 44 (2): 109-14; Mar-Apr 1994). Chemoprevention is an emerging field in oncology. De Palo, etal (Drug Saf, Oct 1995, 13(4):245-56), defined chemoprevention as "the reduction of cancer incidence by pharmacological means through the suppression of established malignant cell clones or alteration in growth and progression of malignant cell populations." Chemoprevention may be applied to the primary, secondary and/or tertiary prevention of cancer (see Exhibit 5). Recent therapeutic advances include dose-intensive combinations, targeted therapy using immunologic or ligand-driven vehicles (Hortobagny GN, Semin Oncol 22 (5 Suppl 12): 101-7; Oct 1995), treatment of dysplastic lesions (Lipkin M, Int J Cancer 69 (1): 64-7; Feb 20, 1996), and novel drug delivery approaches. Tailoring drug affinity for target tissues through genetic and immunologic manipulations introduces the possibility of administering doses above accepted levels of clinical tolerability without danger of toxicity.

RCTs in adjuvant therapies evaluate approaches to prevent recurrence and secondary spread (cytotoxic and hormonal chemoprevention) after a patient has been successfully treated. For instance, finasteride and tamoxifen are adjuvants that block induction of male and female hormones (androgen and estrogen) on prostate and breast cancer growth and are used to contain cancer dissemination outside these organs.

RCTs in neo-adjuvant therapies evaluate treatments designed to reduce disease to a point where it can be treated using standard modalities to preserve the affected organ. Neo-adjuvant treatments rarely increase survival but may improve QOL.

RCTs in Advanced Disease

The prospect of obtaining large effects from health interventions in oncology has been replaced by more realistic expectations (Gray R, etal, Eur J Surg Oncol 21 (2): 137-9; Apr 1995), and the need for larger trials is starting to be recognized as a necessity in order to identify even minuscule improvements in the management of advanced cancer (Peto R, etal, J Clin Epidemiol 48 (1):23-40; Jan 1995 and Horwitz RI, J Clin Epidemiol 48 (1): 41-4; 1995). As patients with more advanced disease are recruited, use of interventions considered experimental increases, treatments become more intense and investigators are faced with increasingly complex ethical questions that often limit trial feasibility. RCTs investigating palliative approaches face the biggest challenge compared to other cancer RCTs regarding patient recruitment:

- usually there are fewer participants in palliative trials
- patients have higher rates of morbidity, and overall and cancer-specific mortality
- patients experience more frequent toxic side effects related to disease and treatment
- participants require more care-intensive protocols

RCTs in Supportive Care

Treatment of cancer often involves an array of supportive agents that are used to mitigate direct adverse effects associated with primary drug and/or radiation treatment approaches (e.g. nausea and vomiting, cardiovascular toxicity, neutropenia, infection, hypercalcemia, etc.). RCTs are routinely used to evaluate the most effective approaches to treat such complications as well as other supportive approaches as nutrition, psychosocial counseling, QOL issues, etc.

New Therapeutic Technologies and RCTs

RCTs will be critical in evaluating new therapies. However, expected approval of more chemotherapeutics with marginal benefits will make it increasingly difficult to recruit early stage cancer patients for RCTs. In some cases, when treatment targets are narrowly defined, effectiveness may be demonstrated without the need for comparisons, rendering RCTs unnecessary.

SURROGATE ENDPOINTS

Surrogate endpoints are response variables that can substitute for the "true" endpoint, for the purpose of comparing specific interventions or treatments in a clinical trial (Fleming TR, etal, Stat Med 13 (9): 955-68; May 15, 1994). The rationale for the use of intermediate endpoints in oncology RCTs is related to the long, natural history of the disease, the paucity of data from RCTs and the need for more direct evidence of treatment efficacy, among others.

The use of markers in populations with cancer risk or early carcinogenesis involves determination of inherited or acquired susceptibility, environmental exposure to carcinogens and their biological effects, and the presence of pre-malignant or primary tumors (Helzlsouer KJ, Cancer Res 54 (7 Suppl): 2011S-2014S, Apr 1, 1994). Serological markers can also be applied to monitor treatment adherence, assess therapeutic benefits, determine who can benefit from more intensive and aggressive treatment strategies, verify cancer eradication, regression, elapse and dissemination, predict survival, etc. Primary prevention is another area where markers are used in RCTs as surrogate measures for genetic susceptibility, pre-cancerous conditions and primary cancer screening. Although RCTs on genetic susceptibility are not anticipated at present, there is increasing societal pressure to address the legal, ethical and financial implications of conducting screening trials on genetic susceptibility in healthy individuals.

A crucial step in the development of cancer markers is their validation. Confidence in serological markers, to be used in major public health initiatives, will only be established from findings supported by RCT results (Greenwald P, etal, Int J Cancer 52 (2): 189-96; Sep 9, 1992). The use of surrogate measures must be supported by evidence linking the mechanism of action of an intervention to a primary endpoint. Interventions may affect more than one biological pathway or mechanism not related to the endpoint of interest. Therefore, when considering the use of intermediate end-points for RCTs, it is also necessary to account for additional benefits and side effects associated with an intervention.

Exhibit 5
Patient Selection and Randomization Criteria in Oncology RCTs

Selection/ Randomization Factors	Description and Comments
Observational Variables	
Age	Oncology RCTs both select and randomize for age; age is a very important variable in cancer in terms of progression outlook, response to medication and QOL, among others; parenthetically, childhood cancers are almost always considered separately
Sex	Oncology RCTs randomize for sex unless the cancer occurs exclusively in one sex; gender may play a role in a patient's response to certain medications and in the nature of such a response; there have been several cases where qualitative differences were observed that were determined by gender
Race	Oncology RCTs attempt to include race as a selection/randomization variable but inclusion of non-whites has been very challenging in the past
Socioeconomic status	Socioeconomic status is often ignored as an RCT variable because of difficulties in recruiting patients who are poor or disadvantaged; however, lack of adequate inclusion of subjects with diverse socioeconomic background compromises application of RCT findings to the general population
Ethnicity	Ethnicity is often disregarded as an RCT variable because of religious, cultural and language bariers in recruiting RCT participants; lack of adequate inclusion of patients from various ethnic backgrounds compromises application of RCT findings to the general population
Overall health status	RCTs usually select for acceptable health status in order to ensure that the patient would be able to withstand the rigors of the treatment; lack of inclusion of patients with poor health status usually compromises application of RCT findings to the general population
Treatment history	RCTs may select patients depending on their previous treatment history
Other variables	Variables associated with certain conditions (e.g. menopause status in females, hormone-positive versus hormone-negative cancer) are used in patient selection and/or randomization
Derived Variables	
Disease history	It may be impossible to randomize patients based on how long they have had the disease
Disease type and stage	Disease type and stage are extremely important selection criteria; often, inappropriate staging caused by failure to detect certain disease attributes clouds RCT results; newer staging approaches may improve accuracy in this area
Prognostic factors	Prognostic factors (molecular markers linked to more aggressive disease, multiple drug resistance, heritable genetic mutations, etc), especially those derived from newly discovered molecular markers, are just beginning to emerge as patient selection criteria
Intrinsic factors (drug allergies, immune status, etc.)	Selection of patients based on previous knowledge regarding allergic reactions to medication or immune status regarding a treatment prevents midstream problems

The prospect of adopting response rates as intermediate endpoints in the approval of oncology drugs is likely to accelerate validation of serological markers of cancer and drug activity. Increasing the availability of methods which can facilitate surrogate evaluations will expedite drug development by helping prioritize promising agents, determine early efficacy, and reduce overall approval time.

Serological markers can provide information on cancer stage and facilitate primary, secondary and tertiary cancer interventions.

CHALLENGES IN INTERPRETING RCTS

There are two sources of error in RCTs:

- systematic (which can be avoided)
- random (which is unavoidable but can be controlled)

Validity is defined as lack of systematic error, and precision as lack of random error in establishing an effect (Rothman KJ, Modern Epidemiology, Little, Brown and Company, 1986). Precision refers to the degree of confidence that an observed effect (or its absence) is an estimate of the true effect. For example, RCTs enrolling insufficient numbers of participants may fail to arrive at an accurate conclusion. Systematic bias affects the internal (accuracy) and external (reliability or applicability) validity of study results. Such bias affects accuracy of results through circumstances related to the setting in which the experiment was conducted. Bias occurs if :

- patient selection influences the outcome of interest
- the index and/or control intervention(s) is/are administered to the wrong group (dilution and contamination crossovers)
- outcomes are not accurately measured (patient misclassification)
- intervention assignments are incorrectly ascertained

In order to arrive at valid conclusions on a given intervention, it is necessary that RCTs are based on accurate determinations of cancer risk or stage. When ancillary methods fail to detect, or erroneously determine cancer progression, the inclusion of these patients in cancer trials may under- or over-estimate their effect and generate erroneous conclusions about the true impact of an intervention. For instance, several studies (Peters WP, etal, J Clin Oncol 11: 1132-43; 1993; Gianni AM, etal, Proc AM Soc Clin Oncol 11:161; 1992, Abstract No 68; Peters WP, etal, Proc Am Soc Clin Oncol 14:316; 1995, Abstract No 933; Gianni AM, etal, Proc AM Soc Clin Oncol 14:90; 1995, Abstract No 61) have reported improvements in disease-free and overall survival in women with Stage II or III breast cancer and poor prognosis (ten or more positive axillary nodes) treated with high-dose chemotherapy and autologous bone marrow transplantation (autoBMT). All of the above studies were small, used patient subsets and based participation on referrals. To determine whether screening methods may have influenced the results, investigators (Crump M, etal, J Clin Oncol 14 (1): 66-69; Jan 1996) compared results of diagnostic tests in patients who were recruited for an autoBMT RCT versus those on standard therapy. Conventional screening (chest x-ray, bone scan and liver ultrasound) failed to detect occult metastatic disease in 23% of participants (N=30) during a two-year period. These cases were detected by head, chest, abdomen or pelvic CT scans, or bilateral bone marrow biopsies.

GENERATING ACTIONABLE INFORMATION FROM RCTS

In most cases, therapeutic advantages in oncology can be demonstrated only by RCTs. As noted throughout this report, the nature of their inquiry is to assess the intervention itself and not the circumstances in which it would be delivered. RCTs usually compare a novel treatment to the clinical standard. If no standard of care is available, or the treatment is compared to an adjuvant, the comparator may be no intervention (e.g., a diagnostic method) or placebo. RCTs can determine that a new cancer intervention:

- is inferior in every aspect to the standard of care
- exhibits better efficacy and QOL
- exhibits equal efficacy but worse QOL
- is equivalent to the standard of care
- is better than no intervention or placebo

RCTs may be conducted after a therapeutic or screening procedure has been incorporated into medical practice, but their impact decreases as the use of the intervention increases. Also, major limitations arise when trying to re-assess methodologies that are part of standard practice. Some of the barriers for conducting RCTs in these settings include ethics of randomizing patients to a treatment strategy of a similar or possibly inferior benefit and strong patient preferences for a certain intervention, especially a new approach with the potential of improving outcome.

For instance, since the 1970s, frequent cystoscopy follow-up with transurethral resection of bladder tumor recurrence has been standard practice in superficial transitional cell cancer (TCC) of the bladder, the earliest stage of bladder carcinoma. Cystoscopy follow-up is recommended at three-month intervals for the first two years, biannually the following year and annually thereafter. The possibility of a less intensive follow-up has been recently considered in a non-randomized study (Killbridge KL, etal, Proc Amer Soc Clin Oncol Vol 15; May 1996, Abstract No 931). Similarly, despite the controversy started in 1993 when the NCI reversed its stance on mammography recommendations for women in their forties, this procedure has become part of the routine annual visit for women at risk of breast cancer.

Clinical Meaning of RCT Results

Assuming that the planning, patient selection, implementation and analysis of RCTs is taken at face value (i.e., no random or systematic error). The central question becomes how this evidence can be translated into the management of the cancer patient. One of the most common misconceptions of RCTs is that findings can be replicated by ensuring an adequate representation of the general population (Roberson NL, Cancer 74 (9 Suppl):

2687-91; Nov 1 1994; Trimble EL, etal, Cancer 74 (7 Suppl): 2208-14; Oct 1 1994; Swanson GM and Ward AJ, J NCI 87 (23): 1747-59; Dec 6, 1995). Despite their role in evaluating interventions, RCT findings rarely guide the practitioner in his search for the best option for each one of his cancer patients.

CURRENT CHALLENGES IN CONDUCTING RCTS

The advantages and limitations of RCTs must be assessed in the context of logistical and ethical issues, health care reform, regulatory policy and transfer of new technologies into clinical practice. A number of barriers prevent the more frequent use of RCTs in oncology. They include issues of a methodological, ethical, regulatory and, increasingly, political, social, economic and cultural nature (Green SB, etal, Workshop on Clinical Trial Issues: Controversies and Pitfalls, 32nd ASCO Annual Meeting, May 18-21, 1996, Philadelphia, PA). The FDA's intention to accept tumor shrinkage as a pre-approval RCT study endpoint, as well as requirements to conduct confirmatory phase IV trials, opens a window of opportunity for additional endpoints and extending follow-up of patients participating in pre-approval trials. These circumstances may contribute to shape the current RCT model into a more affordable and practical mechanism of scientific inquiry.

Costs

Cost remains one of the major barriers for RCTs, and often affects decisions regarding trial size, choice of diagnostic procedures and other issues. For example, staging with less accurate diagnostic tests or starting a trial at the time of cancer diagnosis (as opposed to patient screening) may not only determine the feasibility of a trial but influence its credibility. Because other factors are at stake, a careful evaluation of the trade-off between cost and validity is required. Schwartz, etal (Schwartz JS, Prostate Cancer Intervention Versus Observation Trial: Economic Analysis in Study Design and Conditions of Uncertainty, Monogr NCI (19):73-5; 1995), have advocated use of economic analysis to assess the cost-effectiveness of these decisions. RCTs are not only limited by funding availability. There are barriers involving the health care system, industry, providers, institutions and patients. They include, but are not limited to, inadequate reimbursement of patient care, uncertain market for the development of chemopreventive drugs, lack of provider-equitable compensation, fear of losing patients, and protocol intensity resulting in toxicity and higher patient out-of-pocket expenses.

Ethical Considerations

Ethics of randomization remain at the heart of RCTs. Peto, etal, have advocated the use of the "uncertainty principle" for addressing simultaneously ethical and methodological limitations of RCTs (small size, sample homogeneity and protocol complexity). Their view is that patients cannot chose treatments at random if there is a reasonable certainty about personal or provider preferences. Although the principle certainly questions the ethics of randomization when there is a perception of benefit, it overlooks a number of issues which may further reduce participation. Enrollment in RCTs is sometimes regarded by cancer patients as a "lottery" to get an experimental therapy. It is not unreasonable to assume that patients may base their preference on the expectation that the new intervention is comparatively better, or at least equal to the alternative, rather than on the extent of pre-clinical or early drug trial evidence. Similarly, it forces providers to make recommendations based on incomplete evidence or guesses.

Other Limiting Factors

Randomization is not the only factor contributing to low participation rates. Enrollment criteria or prospect of protocol burden can have a similar effect. Moreover, excessive restriction of trial entry could be regarded as unethical because the possibility of receiving a potentially beneficial treatment is denied. Uncertainty about treatment response or the risk of serious side effects influences, in one degree or another, all RCT participants. The real question is what criteria should be developed to define trial entry for cancer interventions, what information needs to be provided to potential participants, and what should be the role of providers offering advice to patients considering enrollment. As consumers become better informed about new technologies, the debate surrounding this issue intensifies. A recent news article in London's *The Independent* (May 30, 1996) reported that a large number of trials proposed by the UK's Medical Research Council were being abandoned because patients are asking for treatments, not experiments.

RCT ALTERNATIVES

There has been an increasing interest in other forms of assessment in light of costs, complexities, low participation, uncertain reliability, variable public perception, incomplete endpoints and other RCT barriers. The emergence of evaluative clinical sciences (including database analysis and outcomes research) is often viewed as an attempt to replace RCTs as a preferred clinical research method. Those faced with frequent medical decisions, either as chronic patients or practitioners, fully understand the burden of the large, and usually contradictory, information in the clinical trial literature. Decisions need to be made on a daily basis and cannot wait for the completion of RCTs. These decisions depend on the availability of less rigorous methods aimed at providing provisional evidence. It is often argued that RCTs can neither keep the pace of scientific discovery nor adequately deal with data limitations about risks and effectiveness of many of the procedures and treatments currently in practice (Hiatt H and Goldman L, Nature 371:100; Sept 8, 1994). Trialists' rebuttal focuses on these differences

being so negligibly small, or modest, that they may be addressed by methods that are potentially subject to moderate bias or error (Peto R and Collins R, Nature 372: 588; Dec 15, 1994). In reality, modeling and other evaluation techniques often use data from RCTs and meta-analyses as best-case scenarios. The opposite is also true, as users of RCT data often make deterministic assumptions regarding RCT evidence. The main objection to experimental methods is not their accuracy but their relevance. Although the need for scientific rigor is an accepted fact, the issue of interpretation is multidimensional and involves cost, effectiveness, QOL and other measures for which RCTs would be prohibitive.

RCTs, meta-analysis (MA) and health economic modeling are methods with different premises and rationale. Although they are based on different assumptions, the distinction between trial-based, modeling and other studies is sometimes regarded as artificial. A presumption of correspondence is made when RCT evidence is translated into clinical practice and for projecting costs and outcomes beyond the period observed in the RCT (Drummond MF, The Future of Pharmacoeconomics, Quality-of-Life and Pharmacoeconomics in Clinical Trials, Chapter 127: 1225-28, Second Edition, Edited by Bert Spilker, Lippincott-Raven Publishers, Philadelphia 1996). Health economic models rely heavily on the use of multiple sources of information (randomized and non-randomized studies) and assume that this heterogeneity will "balance" any of their biases. Exhibit 6 summarizes the main differences between randomized and non-randomized studies, MA and health economic models.

Despite the availability of other methodologies, evaluations of new medical technologies rely on results from RCTs (Peters WP and Rogers MC, NEJM 330 (7): 473-7; Feb 17, 1994). When a new treatment convincingly improves survival rates or QOL, it becomes the standard of care if its side effects are acceptable and its cost is not prohibitive. The relatively quick assimilation of new technologies into clinical practice illustrates the high level of credibility of RCTs as a method of scientific inquiry. However, new technologies rarely enter the market with sufficient evidence on effectiveness and cost.

Large, simplified RCTs (LSRCTs)

LSRCTs may represent an alternative means of improving the efficiency of RCTs without escalating their costs by increasing the number of participants, extending follow-up and reducing visit intensity, protocol rigidity and per capita expenditure. Although these are desirable goals, the need for increasing understanding on new interventions raises questions about the feasibility of implementing such trials and, again, the reliability of their results. One way to address the first is to demonstrate the cost-effectiveness of LSRCTs. Measures to increase reliance on findings include protocol simplification, increasing group heterogeneity and follow-up, and consideration of other measures, including costs.

The assumptions of LSRCTs are as follows:

- real differences between two interventions are small or moderate
- demonstration of even a small difference may be worthwhile
- small variations can be expected among other patient groups but no reversal in benefits
- biases and random errors can affect the detection of these differences and must be avoided

Several advantages can be derived from adding an economic component to LSRCTs (resources used by the trial and/or consumed by the interventions). The internal validity of the trial is not affected (Baker AM, Practical Aspects of Designing and Conducting Pharmacoeconomic Studies, Chapter 115: 1113-1121, Quality-of-Life and Pharmacoeconomics in Clinical Trials, Second Edition, Edited by Bert Spilker, Lippincott-Raven Publishers, Philadelphia 1996), and economic questions can be implemented alongside clinical protocols. The main limitation is that assessments are limited to the trial and do not reflect the long-term, economic consequences of treatment (Weeks JC, Economic Considerations in Comparing Whole Abdominal Radiotherapy with Combination Doxorubicin-Cisplatin Chemotherapy in Advanced Endometrial Carcinoma: How Much Economic Data Should be Collected? Monogr NCI (19): 17-9, 1995). However, from the perspective of the potential user of LSRCT information, the purpose of using cost-analyses in these settings is to facilitate the economic understanding of the intervention. For example, use of an agent which demonstrates superior benefits and earlier clinical advantages for a chronic condition may result in long-term savings. Therefore, a cost component in LSRCTs represents an intermediate measure of the economic impact of an intervention.

Meta-Analysis

Meta-analysis (MA) of RCTs is the process of using statistical methods to pool and synthesize RCT results and to identify their overall trend (A Dictionary of Epidemiology, Edited by John M Last, Oxford University Press, Third Edition, 1995). MA is being used to clarify disagreements and to interpret the overall RCT evidence from conflicting results from mainly small size RCTs. MA is based on the assumption that synthesis of RCT findings eliminates contradictory results, that the "pooled" population participating in RCTs is homogenous, and that all RCTs included in the MA have a similar protocol. The more the numbers of individual RCT results incorporated in the meta-analysis the greater the likelihood of avoiding serious errors. MA has not solved the problem of clinical translation, and this method has been forced to withstand various criticisms, from skepticism to vigorous objection (Spitzer WO, J Clin Epidemiol 48 (1): 1-4, 1995).

Exhibit 6
A Comparison of Clinical Trial Research Methodologies

Design/ Paradigm	Information Source	Measure	Assumptions	Strengths	Weaknesses	Alternative Approaches
Randomized/ "controlled experiment"	Intervention and control groups	Intervention-response	Subjects and reference population are similar; results can be extrapolated and projected beyond trial boundaries	Accuracy	Reliability; high cost, especially for multi-center studies; random error in smaller trials	Large, simplified RCTs; economic analyses alongside RCTs; use of intermediate endpoints or surrogates including markers
Non-randomized/ "natural observational"	Exposed and non-exposed cohorts, diseased and non-diseased individuals	Association, sometimes cause-effect	Subjects are similar until occurrence of exposure or outcome; results usually require confirmation	Observation of natural events; practicality; feasibility	Results susceptible to bias; may be generalized only via confirmatory studies; moderate cost	Large, simplified longitudinal studies
Meta-analysis/ "pooled analysis"	Published and unpublished RCTs and observational studies	Synthesis of study results	Homogeneity of pooled data; aggregation increases reproducibility of results	Summary of research evidence; low cost	Reflects biases of primary research	Cumulative meta-analysis (new meta-analysis every time results of a new study become available)
Health economic model/ "evaluative or decision-making research"	RCTs and observational studies (published and unpublished); clinical, data, insurance claims, cancer registry and drug databases; census, survey and regulatory data; case reviews; drug literature; etc.	Assessment or projection of outcomes and costs	Defined by the perspective of the analysis; "approximate evidence is better that no evidence"	Evaluation of different scenarios; low to moderate cost; some assessments can be "piggy-backed" onto other studies; exploratory analyses	Results require update and confirmation	Permutation tests

Meta-analysis has grown in popularity over the past decade, primarily because of the need to provide an overall summary of the findings of numerous RCTs on the same topic, to consolidate findings of RCTs of marginal statistical significance and, perhaps, identify moderate effects that would not be discernible in the small individual RCT. In effect, MA wants to analyze isolated RCTs as if they were part of a large multi-center trial. Such an assumption is, however, dangerous because multi-center RCTs adhere to certain protocols and standards of care that may not have been incorporated in the diverse RCTs included in the MA.

Health Economic Models

Health economic models, like all modeling exercises, are retrospective, i.e., the information already exists, or, in its absence, it represents someone's educated guess or group consensus. Their main disadvantage is the potential for reaching a desired result by either missing or omitting information, or assigning unrealistic importance or weight to variables of unknown or contested magnitude. However, when conducted appropriately, health models can be suitable tools to address research gaps, evaluate complex health problems for which RCTs or non-randomized studies are not a suitable option, or forecast costs and outcomes and facilitate decisions at the user, institutional, policy and other levels. To date, the use of health models remains controversial but continues to increase.

Monte Carlo Simulations

Monte Carlo simulations or permutation tests are being increasingly used as an exploratory tool of data sets from randomized and non-randomized studies, as well as predictive models. In these computer simulations, artificial data sets (hundreds to thousands) are created to compare the test statistic of randomly rearranged data with that observed in the study (parametric or non-parametric tests). The null hypothesis is that the observed association is due to chance. If the true test statistic is

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greater than 95% of the values obtained via random simulations, then the null hypothesis of no association (i.e., association by chance) is rejected. Used in the context of RCTs, this alternative does not solve the inference problem mentioned above, because the same information collected in the trial is used as input. This is like trying to improve the quality of wine by investing heavily in machinery but ignoring the grape. No matter how advanced computing power becomes, if there are biases in the original data, conclusions will reflect those biases.

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