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Therapy-associated Solid Tumors

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As survival after a diagnosis of cancer improves, characterization of the late sequelae of treatment becomes critical. The development of second malignant neoplasms represents oneo f them ost serious sideeff ects of treatment withr adiationa nd chemotherapy. Although secondary leukemia was thefi rst reportedc arcinogenic effect resulting from cancer treatment, solid tumors now compriset he largest second tumor burden in some populations of survivors. It should be recognized, however, that solid cancers do not necessarily represent an adverse effect of therapy, but may also reflect the operation of shared etiologic factors, host determinants, gene-environment interactions, and other influences. Quantification of second cancer risk is important in terms of patient management, enabling clinicians to make informed decisions with regard to optimal treatment of the initial cancer, balancing efficacy against acute and chronic sequelae. This article focuses on selected highlights and recent developments in treatment-associated solid malignancies, with emphasis on radiotherapy and chemotherapy in adults, and summarizes areas for future research. Although cancer therapy represents a double-edged sword, it should always be recognized that it is advances in treatment that are largely responsible for the tremendous improvement in patient survival. Thus, the benefit derived from many cancer therapies far outweighs any risk of developing a second cancer.

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As survival rates after diagnosis of cancer improve, identification and quantification of the late sequelae of radiotherapy and chemotherapy become critical. One of the most serious side effectso f cancer treatment is the induction of a new malignancy, which can have a significant impact on patient morbidity and mortality (1, 2). Although secondaryle ukemias were the first reported carcinogenic effect of cancer treatment (3), solid tumorsn ow comprise the largest second tumor burden in some populations (4). Following treatment for Hodgkin's disease, Hoppe (4) estimated that the absolute risk of solid tumors exceeds that of leukemia, i.e. 48.8 and 17.7 excess cases per 10000 patients per year; in some clinical series with long-term follow-up, mortality due to second cancers is now the most common cause of death after Hodgkin's disease itself (4). Among 20-year survivors of Hodgkin's disease reported to population-based cancer registries which comprise the US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program (1973–1998), solidt umors andc ardiovascular disease constitute the most frequent causeso f death (61 and 54 excessc ases per 10000 patients, respectively).

The proportion of second or higher order invasive cancers reported to the SEER Program has steadily increased over the past 25 years. In 1973, second cancers comprised approximately 6% of all cancers. In 1998, the most recent year for which cancer statistics have been compiled, 115734 new invasive cancers were reported. Of these, second or higher order neoplasms accounted for 15.1%, representing 17470 cases. The burgeoning number of multiplep rimary cancers underscores the clinical and public health relevance of these neoplasms. Characterization of second cancer risk is especially important in terms of patient management, enabling clinicians to make informed decisionswit h regard to optimal treatment, balancing efficacy against acute and chronic sequelae. It should be recognized, however, that second cancers might not necessarily represent an adverse effect of radiotherapy and chemotherapy, since numerous factors can contribute to their occurrence (see Fig. 1). These determinants include lifestylech oices such as tobacco, alcohol, and diet; environmental causes; host factors such as genetic susceptibility, immune function, and hormonal status; and interactions between influences. Nonetheless, studies of second cancers provide a singular opportunity to explore carcinogenesis, since patients are exposed to measured amounts of potentially cancer-inducing agents, and dose-response relationships with radiation and chemotherapy can frequently be defined.

Since van Leeuwen & Travis (2) recently published a comprehensive review of multiple primary cancers, this article focuses on highlights and recent developments in treatment-associated solid malignancies, with emphasis on radiotherapya nd chemotherapy in adults. The reader is

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referred to other compilations of the literature (2, 5–7) for additional information.

RADIOTHERAPY

The late carcinogenics equelae of ionizing radiation have beenext ensively documented for moret han five decades, based in large part on studies of occupationally exposed workers, the atomic bomb survivors, and patients either exposed to radiation through diagnostic procedures or given radiotherapy for malignant or benign diseases (8–10). Although most types of solid tumors can be caused by ionizing radiation (10), body tissues differ with regard to cancer susceptibility, with the thyroid gland, female breast and bone marrow the most radiosensitive (9–11). Solid tumors typically occur 10 or more years after irradiation (8, 10), although excess second cancers at selected sites have been detected as early as 5–9 years after exposure (2, 12, 13).

A large number of studies to date have evaluated the risk of solid tumorsfo llowing radiotherapy for Hodgkin's disease (2, 14). Site-specific excesses have been reported for a number of solid cancers, including tumors of the breast, lung, and the gastrointestinal tract. Of particular concern are the large risks of breast cancer that have been observed among young women with Hodgkin's disease (15–18). For patients treated for Hodgkin's disease before age 30, overall 6–7-fold risks of breast cancer ensue (15, 18), whereas risk after age 30 seems either minimally elevated (O/E 1.43; 95% CL 1.0–2.1) (18) or negligible (15). Remarkably increased6 0- to 75-fold risks of breast cancer haveb een reported in girls treated before the age of 16 for Hodgkin's disease (16, 18). Manyo f these patients, who developed breast cancer at a median age of only 31.5 years, received mantle radiotherapy (16), which frequently includesexp osure to the breast area. Thus, increased risks of breast cancer among young women with Hodgkin's disease reflect the well-known sensitivity of the breast to ionizing radiation in youth (10, 19). There are few studies, however, that quantify the risk of breast cancer after Hodgkin's disease in terms of radiation dose to tumor site or consider either the influence of establishedr iskfa ctors for breast cancer on radiation-relatedexce sses or the possibly ameliorating influence of alkylating agent-related menopause. These

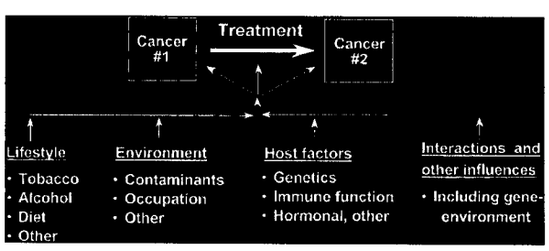

Fig. 1. Schematicillu strationo f riskfa ctors for secondp rimary cancers (refer to text).

issues are being addressed in a large international case-control study led by the US National Cancer Institute, which focuses on treatment-related breast cancer in women diagnosed with Hodgkin's disease at age 30 years or younger.

Lung cancer is one of the most common tumors following Hodgkin's disease (4), with risks elevated as early as 1 to 4 years aftert reatment and persistent for several decades (2, 13, 20). Ionizing radiation is a known lung carcinogen (10), whereas the effect of chemotherapy is more controversial (21–23). In collaboration with The Netherlands Cancer Institute and population-based cancer registries in Iowa, Denmark, Finland, Sweden, Ontario, and New Jersey, the US National Cancer Institute recently completed a case-control study of lung cancer among 19046 Hodgkin's disease patients (1965–1994) (24). Total dose of cytotoxic drugs, radiation dose to the specific location in the lung where cancer developed, and tobacco use werec ompared for 222 patients who developed lung cancer and 444 matched controls who did not develop lung cancer. A radiation dose of 5 Gy or more was associated with a significant overall 6-fold excess of lung cancer, and increased with doses of up to 40 Gy or more (p trend < 0.001) (see Table 1). Treatment with alkylating agents without radiotherapy, however, was also associated with a significant 4-fold excesso f lung cancer, and risk increased with increasing number of cycles (p trend < 0.001). To our knowledge, this largec ollaborative international study is the only investigation of lung cancer following Hodgkin's disease(2 1–23) that simultaneously includes measures of radiation dose to the location where the lung cancer was diagnosed, the cumulative amount of alkylating agents, and information on smoking habits. Findings with regard to alkylating agents and lung cancer risk in thisin vestigation (24) are discussed in more detail in ala ter section of this article.

Patients with Hodgkin's disease experience significantly increased 2 to 11-fold risks of gastric cancer (13, 25–27), withexces ses frequently attributed to prior radiotherapy. The stomach is a known site of radiation carcinogenicity (10), and estimated radiation dosest o the stomach during mantle or inverted-Y radiotherapy with a treatment dose of 35 Gy are 4.2 Gy and 13.0 Gy, respectively (27). It is noteworthy that the risk of stomach cancer following combined modality treatment for Hodgkin's disease appears significantly greater than the risk following treatment with either radiotherapy or chemotherapy alone (13, 25).

An important issue for long-term survivors of Hodgkin'sd isease is delineation of the site-specific temporal patterno f excess solidt umor risk. In most series (2), the risko f solidt umors increases with time up to 20 or more years after treatment for Hodgkin's disease, a temporal pattern consistent with the late effects of radiation. There are few studies, however, in which risk beyond20

Table 1

Relative risko f lungc ancer in patients withHod gkin's disease accordingto type of treatment, radiation dose, number of cycles of alkylating agents and smoking status[1]

		Patients with lung cancer	Matched control patients	Relative risk	95% CI	*p*-value
A. Treatment for Hodgkin's disease[2]						
Radiation > 5 Gy	Alkylating agents					
No	No	21	98	1.0[3]	–	–
Yes	No	53	90	5.9	2.7–13.5	<0.001
No	Yes	73	135	4.2	2.1–8.8	<0.001
Yes	Yes	52	70	8.0	3.6–18.5	<0.001
Combined modality therapy		21	41	5.4	2.1–14.1	<0.001
Initial RT; salvage alkylating agents[4]		31	29	11.1	4.6–29	<0.001
B. Radiation dose to specific location in lung[5]						
0		72	158	1.0[6]	–	–
> 0–4.9 Gy		22	75	1.3	0.3–4.9	0.69
5.0–14.9 Gy		14	18	4.1	0.7–22	0.12
15.0–29.9 Gy		14	22	2.5	0.1–16.1	0.46
30.0–39.9 Gy		51	87	8.6	2.9–30	<0.001
40.0 or more Gy		26	33	7.2	2.2–28	0.001
C. No. of cycles with alkylating agent chemotherapy[7]						
0		74	188	1.0	–	–
1–4		22	44	4.0	1.3–12.5	0.013
5–8		58	89	6.2	2.6–17.1	<0.001
9 or more		28	29	13.0	4.3–45	<0.001
Unknown number of cycles		11	17	5.3	1.6–17.7	0.005
Any non-cyclic chemotherapy		6	26	1.3	0.2–6.7	0.75
D. Smoking habit 5 yearsp rior to lung cancer[8]						
Never smoker		7	92	1.0	–	–
Current cigarette smoker		135	143	22.6	9.5–65	<0.001
Former cigarette smoker		23	56	5.7	2.2–16.6	<0.001
Cigar or pipe only		10	20	8.9	2.6–32	<0.001
Not stated		24	82	5.0	1.9–15.3	0.001
E. Smoking habit at diagnosis of Hodgkin's disease[9]						
Never smoker		7	83	1.0	–	–
Current cigarette smoker		138	146	21.2	8.6–62	<0.001
Former cigarette smoker		13	34	4.0	1.4–12.5	0.009
Cigar or pipe only		10	17	9.0	2.5–35	<0.001
Not stated		31	113	4.0	1.5–12.3	0.005

Abbreviations: CI = Confidence interval; Gy = gray; RT = radiotherapy.

Source: From Travis LB, Gospodarowicz M, Curtis RE, et al. Lung Cancer Following Chemotherapy and Radiotherapy for Hodgkin's disease. J Natl Cancer Inst 2002;94:182–192, by permission of Oxford University Press.

[1] The table is limited to 199 case patients and 393 control patients with adequate data for reliable radiation dose estimation. Refer to Methodsse ction for details.

[2] Exposure wasd efined as treatment with alkylating agentsfo r more than 1 month or radiotherapy that resulted in ad ose of five or more Gy or moret o thesp ecificlo cation in the lung where thec ancer was diagnosed and the corresponding region in the control patients. All relative risks were adjusted for smoking status. Refer to the Methods section for details.

[3] The reference group consisted of 21 patients with lung cancer and 98 control patientswh o received a radiation dose of less than 5 Gy to the specific location in the lung where the cancer was diagnosed (or the corresponding region in matched control patients) and/or treatment with non-alkylating agent chemotherapy. For 12 case patients and 46 control patients, time since diagnosis of Hodgkin's disease was less than 5 years so that these patients were uninformative for radiotherapy comparisons. Refer to the Methodsse ction for details.

[4] Median time between radiotherapy and salvage alkylating agents was 3.3 years.

[5] Dose of radiation to the specificlo cation in the lung where thec ancer was diagnosed and the corresponding location in matched control patients. All relative riskswe re adjusted for smoking status and number of cycleso f alkylating agents. *P* trend for radiation dose <0.001.

[6] For 46 case patientsa nd 91 control patients in thisca tegory, the time since diagnosis of Hodgkin's disease was less than 5 years so that these patients were uninformative for radiotherapy comparisons. Refer to the Methodsse ction for details.

[7] All relative risks were adjustedf or smoking status andr adiation dose to the specificlo cation in the lung where the cancer was diagnosed and the corresponding location in matched control patients. *P* trend for number of cycles with alkylating agents <0.001.

[8] Represents estimatedt obacco habit five years prior tod iagnosis date of lung cancer andco rresponding date in control patients, utilizing information recorded up to 1 year prior to these dates. All relative risks were adjusted for radiation dose and number of cycles of alkylating agents. For current smokers, the risk of lung cancer at <1 pack per day (PPD), 1–2 PPD, and 2+ PPD was 17, 25, and 70, respectively.

[9] Represents estimated tobacco habit at diagnosis of Hodgkin's disease, using only information recorded up to one year after that date. All relative risks were adjusted for radiation dose and number of cycles of alkylating agents.

years is quantified, and even then, they are typically based on sparse numbers (16, 26, 28–31). To our knowledge, only one large population-based investigation to date has examined second cancer risk 25 or more years after Hodgkin's disease (27). In a multicenter study of over 32000 one-year survivors of Hodgkin's disease, Dores et al. (27) described an overall decrease in the relative risk and absolute excess risk(A ER) of all solidt umors at 25 years, although site-specific risks remained elevated for several cancers, including those of breast, esophagus, stomach and uterine cervix. Compared to the general population, the relative risks for all solid tumors (n = 1726)in the 1 to 9-year, 10 to14-year, 15 to 19-year, 20 to 24 year, and 25 + -year intervals after Hodgkin's disease were 1.6, 2.4, 2.5, 3.0, and 1.8, respectively. After a continuing increase in the relative risk (and AER) of all solid tumors through the 20 to 24-year follow-up period, an apparent downswing in both parameters was evident at 25 years. The decrease was observed in each registry that contributed person-years to this interval, including those with nationwideca ncer registration. Longer follow-up of additional cohorts of Hodgkin's disease patients is necessary to further characterize long-term patterns, and to clarify the effect of age at Hodgkin's disease treatment and attaineda ge on second cancer risk (13, 26, 27, 31). Van Leeuwen et al. (14) recentlyp rovided a review of these issues.

In a number of studies (2) the risk of second cancers among men with testicular cancer is described, but few investigations have quantified long-term risks among large numberso f survivors, taking into account both histologic type of primary tumor and initial therapy. The largest investigation to date included over 28000 one-year survivors diagnosed with a first primary testicular cancer (1935–1993) and reported to population-based cancer registriesin Europe and North America (32). Second cancers were diagnosed in 1406 patients (Observed-to-expected ratio [O/E] = 1.43; 95% CI 1.36–1.51; AER: 16 excess cancers per 10000 men per year), with significantly elevated risks observed for all solid tumors (O/E = 1.4; Obs. = 1251), acute lymphoblastic leukemia, acute non-lymphocytic leukemia, melanoma, non-Hodgkin's lymphoma (NHL), and cancers of the stomach, colon, rectum, pancreas, prostate, kidney, bladder, thyroid, and connective tissue. Risk of solid tumors increased with time since testicular cancer diagnosis, reaching 1.5 after two decades of follow-up (p trend = 0.00002). Among 20-year survivors, significant excesses persisted for cancers of the stomach (O/E = 2.3), colon (O/E = 1.7), pancreas (O/E = 3.2), prostate (O/E = 1.4), kidney (O/E = 2.3), bladder (O/E = 2.8), and connective tissue (O/E = 4.7) (32). Overall second cancer risk was similar following seminomas (O/E = 1.4) and non-seminomatous tumors (O/E = 1.5). Thec umulativer isko f a second cancer 25 and 30 years after the diagnosis of testicular cancer was 15.7% and 22.6%, respectively. The actuarial risk of a second tumor at 25 years was larger for patients with seminomas (18.2%; 95% CI = 16.8–19.6) thanfo r thosewi th non-seminomatous tumors (11.1%; 95% CI = 9.3–12.9), although the disparity is likely due to the older average age of the men with seminomas (39.2 years vs. 29.8 years), since the excess cumulative risks were comparable. The temporal pattern of excess risks and the distribution between treatment groups were suggestive of the late effects of radiotherapy for cancers of the stomach, bladder, and possibly, pancreas. In clinical studies significantly increased 8-fold risks of stomach cancer have been reported following infra- and supra-diaphragmatic irradiation for testicular cancer (33) and 4- to 5-fold excesses after abdominal radiotherapy (34). Analytic data, however, whichd escribet her elation between radiation dose and the subsequent incidence of gastric cancer are sparse (10). Radiation risk estimates are based largely on the Life Span Study of survivors of the atomic bombings in Japan (n = 79972), who demonstrate markedly different underlying cancer incidence rates compared with Western populations.

In general, excess secondt umors of the digestive tract among cancer survivors have not been limited to the stomach, but have included neoplasms of the pancreas, esophagus, and other sites (25–27, 31, 32, 35, 36). Significant 4- to 5-fold excesses of pancreas cancer following radiotherapy areo bserved among long-term survivors of Hodgkin's disease (25) and cancers of the testis (32) and ovary (35), althoughd ata describing treatment fields and dose are not available. Duringt ypical abdominal radiotherapy for these cancers, estimated dosest o the pancreas are high, rangingf rom 20 to 31 Gy (27, 32). Thus, the pancreas does not appear especially sensitive to the carcinogenic effects of ionizing radiation (37) except when very high doses are given (38). The Japanese atomic-bomb data show significant 40% excess risks per gray for esophageal cancer (mean organ dose 0.24 Gy) (39), although elevated riskswe re found only in the early period after exposure (10). In contrast, excesses ophageal cancers occur for at least one decade after radiotherapy for breast cancer (36) and for 20 or morey ears after treatment for Hodgkin's disease (O/E = 19.5) (27). Information on the risk of radiation-associated esophageal cancer by histologic type is sparse (36).

Future research

Important issues for future research include the relation betweenr adiationd ose and solidt umor risk in the high-dose range, site-specific temporal patterns of radiation-inducedc ancer, and the interaction of radiotherapy with other influences, such as lifestyle factors(e. g. tobacco use) and genetic susceptibility. In particular, it is quite likely that genetic factors influence the occurrence of radiation-related solid tumors (40, 41). Germline mutations in tumor suppressor genes confer an increased susceptibility to radi-

ation-related carcinogenesis among patients with hereditary retinoblastoma (40, 42). Wong et al. (40) showed that radiotherapy significantly increased the risk of subsequent tumors in children with hereditary retinoblastoma (50-year cumulative risk 58%, compared with 27% in non-irradiated hereditary patients). Radiotherapy did not significantly affect risk in non-hereditary retinoblastoma patients. The *Rb* gene and others that confer increased susceptibility to radiation damage, sucha s *TP53* (43) and *ATM* (44), are important in thecellu lar responset o DNA damage (45). For patients with germline mutations in *TP53* (Li-Fraumeni syndrome), this sensitivity translates into an increased risk for radiation-associated cancer (43, 46). Olsen and colleagues (47) recently showed that blood relatives of patients with ataxia-telangiectasia experience an increased 1.54-fold (95% CI 0.95 to 2.36) risk of breast cancer, but concluded that, overall, *ATM* constitutes a weak genetic risk factor. Similarly, investigations to date do not indicate that AT carriers account for a substantial proportion of patients with radiation-induced second cancers (48–50). Moreover, it is likely that inherited or acquired mutations in specific genes predispose only a small proportion of cancer patients to subsequent solid tumors.

Genetic polymorphisms of several carcinogen-metabolizingen zymes have been extensivelyin vestigated (51), but only recently have polymorphisms in DNA repair genes been reported in the human population (52). Study of selected polymorphisms in DNA repair pathways at cancer sites for which DNA damaging agents (e.g. radiation) play a pivotal role in carcinogenesis seems an especially promising area for future research. Other factors which are likely to be important in the individual response to radiation exposure include radiation-related genomic instability (53, 54), epigenetic phenomena, and non-targeted bystander effects (55, 56). Given the exponential growth in our knowledgeo f the humangen ome (57, 58), together with the development and application of new molecular methodologies (59, 60) and the emergenceo f proteomics (61–63), a comprehensive research approach into the myriad mechanisms that underlie radiation-related cancer may soon be possible. Advances in our understanding may eventually facilitate identification of susceptible subgroups of the population. In the interim, it may be noteworthy that Nichols and colleagues (48) recently reported that cancer patientswi th ap ositive family history of neoplasia could be at increased risk of second cancers compared with patients who do not develop subsequent tumors. This finding may reflect genetic factors or common environmental exposures, or both influences. Thus, when feasible, future investigations of second cancer risk should incorporate data on cancer in first-degree relatives to confirm this observation(4 8); linkage of family databases with cancer registry files may provide one such opportunity (64).

Futuree ndeavors should also address whether lates equelae may be associated with newer types of radiation treatments, including three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) (65), stereotacticr adiosurgery (66), and radiolabelled monoclonal antibodies (67). Some investigators (65) have cautioned that the goal of delivering larger doses to tumor by meanso f 3D-CRT and IMRT should not come at the expense of increasing the incidence of late sequelae. It is clear that carefully planned studies will be needed to monitor both the acutea nd long-term adversee ffects of 3D-CRT and IMRT, as well as treatment efficacy. Flickinger et al. (68) described non-neoplastic complications resulting from radiotherapyfo r arteriovenous malformation (AVM), showing that symptomatic post-radiosurgical imaging changes (radiation necrosis) were correlated with both 12 Gy volume and AVM location. These investigators pointed out the deficit in long-term data for patients treated with stereotactic radiotherapy, noting that the median patient follow-up in their study was only 44 months(r ange 24–96 months). In another study of complications among 133 patients treated with radiosurgery for brain tumors or AVM (median follow-up 28.1 months), Voges et al. (66) commented on the vulnerability of normal brain tissue to single-dose irradiation, and Ron and colleagues (69) described the occurrence of brain tumors following cranial radiotherapy.

Radioimmunotherapy, or radiolabelled monoclonal antibodies, is efficacious in the treatment of B-cell lymphomas (67). This therapeutica pproach relies on the targeted delivery of radioactive particles(beta-emitters) to the cell surface, with Iodine-131 and Yttrium-90, the most commonly used isotopes. Kaminski (70) recently reported the occurrence of four secondary MDS among 60 patients with NHL treated with iodine I-131 tositumomab (median duration: 35.5 months). All patients, however, had been heavily pretreated with chemotherapy, precluding the ability to tease out any role of radioimmunotherapy in the development of this complication. The major acute toxicity of I-131 tositumomab in this study (70) was hematologic. Erwin et al. (71) were unable to correlate estimated doses of radiation to bone marrow delivered by a Y-90-labelled anti-CD20 monoclonal antibody with hematopoietic toxicity, urging caution in the prediction of hematopoietic side effects based on marrow dose estimates. Given the relatively recent development and availability of radioimmunotherapy, it is clear that additional follow-up will be needed to characterize any long-term sequelae.

CHEMOTHERAPY

A major unresolved issuein second cancer research is to what extent chemotherapy might induce solid tumors, given the known carcinogenicity of cytotoxic drugs in laboratory animals (72). A small increase in the relative risk of a common human solid tumor carries a considerably larger impact in a population than a comparable elevation in leukemia, a rare cancer. Critical questions

include delineation of involved cancer sites, the magnitude and temporal pattern(s) of excessr isk, and clarification of possible interactions with radiotherapy and other risk factors. It is also important to understand the influence of patient age and gender, initial cancer type, underlying host susceptibility, and the role of concomitant medications, including other cytotoxic drugs. For chemotherapeutic agents eventually linked with solid tumors, it will be informative to understand whether the schedule of drug administration (73) or timing with radiation exposure might influence solid tumor risk.

Solid cancers that have shown a dose-dependent relation with the prior administration of cytotoxic drugs include bladder cancer (74), bone sarcomas (42, 75), and lung cancer (24). A strong relation between cumulative dose of cyclophosphamide for NHL and subsequent bladderca ncer risk (p trend < 0.001) has been demonstrated, with risk increasing to 15-fold following cumulative amounts of 50 or more grams (20). Tucker et al. (75)in itially related alkylating agent treatment for childhood cancer to subsequent excesses of bone sarcomas; more recently, Hawkins and colleagues (42) demonstrated that the relative risk of bone sarcomain creases with increasing cumulative exposure to alkylating agents, even after adjustment for radiotherapy. The effect of radiotherapy on sarcoma excesses, however, seems larger than that of chemotherapy. Other investigators (76) have found a significant reduction in the latency period for bone sarcoma among cancer patients treated with both radiotherapy and anthracyclines.

Several studies have addressed the role of chemotherapy for Hodgkin's disease on the subsequent risk of lung cancer (21–24). Kaldor et al. (21) reported that the risk of lung cancer following chemotherapy for Hodgkin'sd isease was 2-fold compared with patients given either radiotherapy only or chemotherapyp lus radiotherapy. Although lung cancer excesses did not increase with cumulative number of chemotherapy cycles, Kaldor et al. (21) concluded that cytotoxic drugsgiv en to treat Hodgkin'sd isease might be at least as carcinogenic to the lung as radiotherapy. Van Leeuwen et al. (22) found no association between chemotherapy for Hodgkin's disease or number of cycles and lung cancer risk. Swerdlow et al. (23) reported ar isk of 1.66 for lung cancer following treatment with mechlorethamine,vin cristine, procarbazine, and prednisone (MOPP) in British patients with Hodgkin's disease, but no difference in risks for one to six or seven or more cycles was evident, and informationo n cumulativea mount was not available. Of the above investigations (21–23), only the study by van Leeuwen et al. (22) contained detailed data on smoking habits. Information on tobacco use was available for 39% of subjects in the Britishs tudy (23) and5 9% of patients in the investigation by Kaldor et al. (21). None of the above investigations was able to address the interaction between radiotherapya nd chemotherapy on lungca ncer risk or assess long-term temporal patterns. In the multicenter study (24) briefly described earlier in this paper, alkylating agents for Hodgkin's disease were shown to increase the subsequent risk of lung cancerin a dose-dependent manner. Among patients treated withM OPP, risko f lung cancer increased with cumulative amounts of both mechlorethamine and procarbazine ($p < 0.001$) when evaluated separately. Lung cancer excesses also followed therapy witho ther alkylating agents (RR 6.3; 95% CI 2.5–17.7). After treatment with alkylatinga gents and radiotherapy together, the risk of lung cancer was as expected if individualexces s relative risks (RR) were summed (RR = 8.0; 95% CI 3.6–18.5). Tobacco use increased lung cancer risk 20-fold; and data were compatible with am odel in which risks from smoking multiplied the risks from treatment. Significantly elevated risks of lung cancer were apparent as early as 1–4 years after alkylating agent treatment, while excesses after radiotherapy began after 5 years and persisted for over 20 years. Significantly increased 6-fold and 9-fold risks of squamous cell and small cell lung cancers followed alkylatinga gent therapy, and non-significant 3t o 4-fold excesses for adenocarcinoma and large cell carcinoma were also observed. Significantly increased 8 to 14-fold risks for all major histologic types of lung cancer occurred after radiotherapy.

Mechlorethamine, procarbazine, and chlorambucil are carcinogenic to rodent lungs(7 2), and mechlorethamine is related in chemical structure to sulfur mustard, a human lung carcinogen (77). The molecular pathways that might link alkylating agent administration to later excesses of lung cancer are not known. In general, alkylating agents achieve their anti-tumor effect by direct reaction with DNA bases (78). Methylating drugs, such as procarbazine, can form the same DNA adduct (O^6-methylguanine) that is generated by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). O^6-methylguanine is mutagenic and carcinogenic (79), with levels of this DNA adduct linearly correlated ($p < 0.01$) with cumulative doses of procarbazine in lymphoma patients (80). NNK is at obacco metabolite that serves as a potent lung-specific carcinogen in laboratory animals (81). Excesses of lung cancer have also been related to impaired repair of O^6-methylguanine adducts (82). It is clear that additional investigations are required to understand the carcinogenic mechanisms (78, 80–86) that underlie the increased risks of lung cancer following alkylating agent therapy for Hodgkin'sd isease (24). It is not clear whether the results reported in patients with Hodgkin's disease can be generalized to patients with other cancers, in view of the immune defects associated with this lymphoma (87) and the highp revalenceo f tobacco use among case patients and control subjects in the aforementioned study (24). Tucker et al. (88) found, however, that alkylating agent treatment for small cell lung cancer (SCLC) may contribute to the risk of a second primary non-SCLC. Lung cancer excesses have also been observed following treatment for other lymphopoietic malignancies such as chronic lymphocytic leukemia (89) and NHL (90).

Future research

Other solid tumors for which the role of antecedent chemotherapy might be explored include gastric cancer in patients withH odgkin's disease (13, 25). N-nitrosoc ompounds are strongly associated with human stomach cancer and may contribute to the induction of esophageal and pancreas tumors (91). For chemotherapeutic agents linked with excesss olid tumors, the effect of interindividual variation in the absorption, distribution, metabolism, and excretion of these drugs and subsequent cancer risk should also be characterized. The influence of polymorphisms in drug-metabolizing genes, including the cytochrome p450 enzymes, glutathione S-transferases, and arylamine–acetyltransferases in chemotherapy-related leukemias was recently summarized (92). Other factors that might have an impact on the development of chemotherapy-related leukemias should also be examined to determine what effect they might have on solid tumors. These influences include germline mutations in tumor suppressor genes; other types of genetic susceptibility; interindividual variation in DNA repair; renal and hepatic function; route of administration(9 3); and the role of concomitant medications. Whether patients with hereditary retinoblastoma might demonstrate an increased susceptibility for chemotherapy-associated carcinogenesis, as they do for radiation-related carcinogenesis (40), should also be examined. Nishimura et al. (94) recently described a one-year-old girl with bilateral retinoblastoma treated with 5 courses of adjuvant chemotherapy (carboplatin and etoposide) following enucleation of the left eye and photocoagulation of the tumor in the right eye. One year after completion of chemotherapy the child was diagnosed with acute myelogenous leukemia-M5, and blasts demonstrated the translocation (t(4;11) q21; q23) with MLL gene involvement.

The interactiono f chemotherapy withr adiation in the development of solid tumors should also be investigated further. Thesein cludet hejo int effect of thesea gents on the magnitude of risk (24, 74), temporal patterns of excesses (76), the influence of the sequence and timing of exposure to these treatments (2, 26), and interactionsw ith other risk factors. It will be important to discern whether any associationsb etween cytotoxic drugs and excess solid tumors represent an independent carcinogenic effect of chemotherapy (24, 74, 95), radiosensitization properties of selected chemotherapeutic agents (96, 97), the possible inhibition of repair of radiation-induced DNA damage by cytotoxic drugs(98), or a combination of these and other possible mechanisms (99). Children (n = 234) given doxorubicin and more than 35 Gya bdominal radiation for Wilm's tumor were found to have a36- fold risk (95% CI 16–72; 8 observed) of second solid tumors, compared with no second tumors observed among children (n = 291) given doxorubicin alone (98). Breslow et al. (98) reasoned that doxorubicinm ight inhibit the repair of radiation-induced damage, perhaps through an effect on DNA topoisomerase II. It shoulda lsob e recognizedt hat genetic predisposition contributes to excess second cancers among children with Wilm's tumor (98, 100).

Cumulative doses of cisplatin for either ovarian cancer (p trend for dose < 0.001)(93) or testicular cancer (p trend for dose < 0.001) (101) have been linked with increased risks of secondaryle ukemia. The strong dose-dependent leukemogenicity of platinum is consistent witht he observationt hat in humans ubjects given cisplatin-basedt herapy, the concentration of cisplatin-DNA adducts increases as a function of drug dose and correlates with clinical response to therapy (102). Cisplatin, however, also induces solid tumors in laboratory animals (72) and persists in numerous tissues, including kidney and brain (as well as bone marrow)lo ng after treatment is completed (103). The current development of oral formulations of platinum (104), which also radiosensitizet issue (105), increases the need to understand the magnitudea nd scopeo f theca rcinogenicity of this widely used cytotoxicd rug. It would seem warranted, then, to extensively follow patients treated with platinum-based chemotherapy (32, 35) in order to clarify their long-term risks of solid tumors. Continued follow-up seems especially critical for men with testicular cancer, given the relatively young age at which this cancer is diagnosed and the resultant lifetime for the manifestation of the late effects of treatment.

The radiation potentiation provided by several cytotoxic drugs, e.g., platinum, 5-fluorouracil, and hydroxyurea, has been well characterized (106); whether these properties might be associated with an enhanced risk of second tumors in cancer patients treated with chemoradiation (107, 108) is not known. For those agents, such as cisplatin, which may have an independent carcinogenic effect (93, 101), the issue of the dose needed for carcinogenesis versus the dose needed to potentiate any radiotherapy-related cancer excesses shouldb e clarified. Although drugs classified as either antimetabolites (72) or nucleoside analogs (109) have not been considered as carcinogenic to humans, Relling et al. (99)r eported that, following cranial irradiation for acute lymphoblastic leukemia, children who had a wild-type or defective thiopurine methyltransferase phenotype had an 8.3% and 42% (p = 0.0077) cumulative risk of brain cancer, respectively. These patients had also received concurrent systemic chemotherapy with high-dose methotrexate and high dose 6-mercaptopurine. The authors hypothesized that the defective enzyme activity may have resulted in higher levels of thioguanine nucleotide metabolites of 6-mercaptopurine during radiotherapy. The finding by Relling and colleagues (99) underscores the importanceo f furthering our understanding of thep harmacogenetics of not only alkylating agents, but other cytotoxic drugs as well (92).

Future investigations should explore whether chemoprotectantsa nd radioprotectantsm ight influence the late carcinogenic sequelae of chemotherapy and radiotherapy. Although Dorr (110) hypothesized that the radioprotectant amifostine might diminish the risk of cancers associated with radiation and selected types of chemotherapy, the acute toxicitya nd expense associated with this drug (111) appear to have limited its use. Lindegaard & Grau (112) recently suggested that the available clinical studies may not possess sufficient statistical power to evaluate the effect of amifostine on the therapeutic indexo f selected treatments. Swain and colleagues (113) reportedt hat the administration of cardioprotectants to patientsgiv en doxorubicin-containing chemotherapy may exacerbate several of the acutes ide effects of treatment, including a significant lowering of the nadir white blood cell count. Whether these types of acute adverse effects will translate into amplification of any late sequelae should be explored, although evidence with regard to the human carcinogenicity of doxorubicin remains conflicting (2).

COMMENT

In summary, this article serves to highlight recent developments in the study of therapy-associated solid tumors. The advancement in our knowledgeo ver the past decade has made it possible to identify radiotherapy and chemotherapy regimens that are followed by a large risk of developing second cancers. Although individual susceptibility factorsr emain unclear, groupso f patientsca n be targeted for closer surveillance. Whenever effective screening methods (e.g. mammographic examination) are available, these should be integrated into patient follow-up. Preventive approaches (e.g. smoking cessation; avoidance of ultraviolet light) may alsor educet her isk of developing selected second cancers, and patients should be encouraged to adopt practices consistent with a healthy lifestyle. Although long-term follow-up clinics exist for survivors of childhood cancer, therea re few mechanisms available to systematically follow survivors of adult cancer (114). The effective constructiono f multidisciplinary clinical and research programs for these patients will require the cooperation of numerousin stitutions, and could serve to further our knowledge not only of treatment-associated cancers, but other late effects of therapy. The burgeoning number of patients withs econdca ncers worldwide serves only to highlight the need for the development of comprehensive survivorship networks that include education programs. Existing resources that might serve as a foundation for survivorship research include population-based cancer registries, regional cancer centers, radiotherapy centers, and clinical trial groups. Moreover, there are now a considerable number of large cohorts worldwide for whom cancer incidence is being determined and for whom information on a variety of cancer risk factors and biologic specimens are being prospectively collected. In the future, these large studies could potentially be harnessed to examines econd cancer risk, particularly the roleo f gene-environment interactions. Althoughc ancer therapy represents a double-edged sword (1), it should always be pointed out that it is advances in treatment that have been largely responsible for the tremendous improvement in patient survival. Thus, the benefit of many cancer therapies far outweighs the risk of developing a second solid tumor.

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