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Melatonin as Adjuvant Cancer Care With and Without Chemotherapy: A Systematic Review and Meta-analysis of Randomized Trials

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Abstract

Background. Melatonin (MLT) is known to possess potent antioxidant, antiproliferative, immune-modulating, and hormone-modulating properties. Clinical evidence suggests that MLT may have a possible role in the treatment of cancer. The authors systematically reviewed the effects of MLT in conjunction with chemotherapy, radiotherapy, supportive care, and palliative care on 1-year survival, complete response, partial response, stable disease, and chemotherapy-associated toxicities. *Methods*. The authors searched 7 databases: MEDLINE (1966-February 2010), AMED (1985-February 2010), Alt HealthWatch (1995-February 2010), CINAHL (1982-February 2010), Nursing and Allied Health Collection: Basic (1985-February 2010), the Cochrane Database (2009), and the Chinese database CNKI (1979-February 2010). They included all trials that randomized patients to treatment, including MLT or a similar control group without MLT. *Results*. The authors included data from 21 clinical trials, all of which dealt with solid tumors. The pooled relative risk (RR) for 1-year mortality was 0.63 (95% confidence interval [CI] = 0.53-0.74; $P < .001$). Improved effect was found for complete response, partial response, and stable disease with RRs of 2.33 (95% CI = 1.29-4.20), 1.90 (1.43-2.51), and 1.51 (1.08-2.12), respectively. In trials combining MLT with chemotherapy, adjuvant MLT decreased 1-year mortality (RR = 0.60; 95% CI = 0.54-0.67) and improved outcomes of complete response, partial response, and stable disease; pooled RRs were 2.53 (1.36-4.71), 1.70 (1.37-2.12), and 1.15 (1.00-1.33), respectively. In these studies, MLT also significantly reduced asthenia, leucopenia, nausea and vomiting, hypotension, and thrombocytopenia. *Conclusion*. MLT may benefit cancer patients who are also receiving chemotherapy, radiotherapy, supportive therapy, or palliative therapy by improving survival and ameliorating the side effects of chemotherapy.

Keywords

melatonin, complementary medicine, integrative oncology, chemotherapy, natural health product, cancer, systematic review, meta-analysis

Introduction

Melatonin (MLT; *N*-acetyl-5-methoxytryptamine) is an indolamine hormone secreted from the pineal gland that is intricately involved in the regulation of human chronobiological and endocrine function.[1] This neurohormone is known to possess potent antioxidant, immunomodulating, oncostatic, antiproliferative, and endocrine-modulating properties.[2,3] Observational studies have linked long-term disruption of circadian rhythm with decreased MLT secretion and increased cancer risk, whereas clinical evidence suggests possible benefit from MLT on survival in patients with cancer.[4]

Disruption of nocturnal MLT secretion in night shift workers has been associated with modestly increased risk for breast and other cancer types.[5-8] A 2005 meta-analysis of 13 observational studies found significantly increased breast cancer incidence among female airline cabin crew (standardized incidence ratio = 1.44; 95% confidence interval

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[CI] = 1.26-1.65) and in female night workers (relative risk [RR] = 1.51; 95% CI = 1.36-1.68).[9] More recently, the International Agency for Research on Cancer reclassified "shiftwork that involves circadian disruption"[10] from a possible to a probable (group 2A) human carcinogen, in recognition of this relationship.

On the strength of these findings, Denmark has become the first country to declare breast cancer an "occupational disease."[11] Danish women with breast cancer have begun receiving compensation if, without any other risk factors, they had been working at least 1 night shift a week for the past 20 years.[10,11] This development highlights MLT as highly relevant not only within the field of medical oncology but also in the area of public health.

As a possible explanation of the mechanism by which MLT may affect breast cancer risk, the melatonin hypothesis suggests that lowered levels of MLT secretion at night may lead to increased estrogen levels and increased turnover of breast epithelial stem cells, with subsequent increased risk of malignant transformation.[12] MLT appears to impact estrogen metabolism through selective estrogen receptor modulator (SERM) and selective estrogen enzyme modulator (SEEM) activity.[13]

In addition to hormonal effects, MLT is thought to possess immunopotentiating and oncostatic effects by increasing the activity of T and B lymphocytes, monocytes, natural killer cells, and immunoactive cytokines (IFN [interferon]-γ, IL [interleukin]-2, IL-6, and IL-12) as well as promoting apoptosis and inhibiting angiogenesis.[2,3] Human intervention trials of MLT for the prevention of cancer are notably lacking; however, studies of MLT for active treatment of cancer have been promising.

In 2005, we published a meta-analysis reviewing 10 human trials of MLT in solid tumor cancers and reported findings of mortality at 1 year (RR = 0.66; 95% CI = 0.59-0.73).[4] Many of these trials were conducted in conjunction with chemotherapeutic agents, including tamoxifen, cisplatin, etoposide, IL-2, and radiotherapy. Although the pooled analysis showed benefit on survival, the impacts of MLT on chemotherapy-induced side effects such as alopecia, asthenia, and thrombocytopenia were not reviewed. This systematic review and meta-analysis updates our 2005 meta-analysis. In addition to updating pooled survival statistics, this review holds special relevance to the use of MLT alongside chemotherapy: it assesses the impact of MLT with chemotherapy on therapeutic efficacy, measured as patient survival, and assesses the tolerability of chemotherapy, measured as the extent of chemotherapy-associated toxicities.

Methods

Eligibility Criteria

To be included in the systematic review, studies had to enroll and randomize cancer patients and allocate them to a treatment regime that included MLT in an active group compared with no MLT treatment in a control group. All additional cointerventions had to be identical in both groups, including the use of chemotherapy, radiotherapy, and supportive or palliative care. Studies that reported only laboratory values rather than clinical responses were excluded from the analysis.

Literature Search

PW and TT worked independently searching the following English electronic databases: MEDLINE (1966-February 2010), AMED (1985-February 2010), Alt HealthWatch (1995-February 2010), CINAHL (1982-February 2010), Nursing and Allied Health Collection: Basic (1985-February 2010), and the Cochrane Database of Systematic Reviews (2009). In addition, PW searched the Chinese database CNKI (1979-February 2010). After initial screening, the full texts of the publications were independently assessed for eligibility by PW, TT, and DAK with consensus agreement used to determine eligibility where possible. Third-party arbitration (DS) was used in the case of any disagreements regarding inclusion.

Data Extraction

Reviewers PW, TT, and DAK conducted data extraction independently using a standard prepiloted form that included basic information on the patients, data on trial quality, protocol details, and outcomes assessed. Information collected on the patients included type of cancer, performance status (using Karnofsky's score), and type(s) of chemotherapy. The quality and risk of bias criteria were extracted and included adequate information on randomization, stratification, allocation concealment, blinding, informed consent, ethics review, sample size calculation, patient flow through the trial, withdrawals, and reporting of adverse events. When methodological issues were not reported, the study author(s) were contacted. The outcome measurements assessed included 1-year mortality, complete response, partial response, and stable disease. In addition, all data on the occurrence and severity of adverse events were extracted. In the case of any disagreements, third-party arbitration (DS) was used.

Data Analysis

The κ value provided a measure of chance-corrected agreement between assessors of eligibility and study quality. We calculated the RRs and appropriate 95% CIs of outcomes according to the number of events in all cancer treatment studies and studies that only included chemotherapy in treatment. In circumstances of zero outcome events in both arms of a trial, we used the Heldane method and added 1 to each arm, as suggested by Sheehe.[14] We first pooled studies

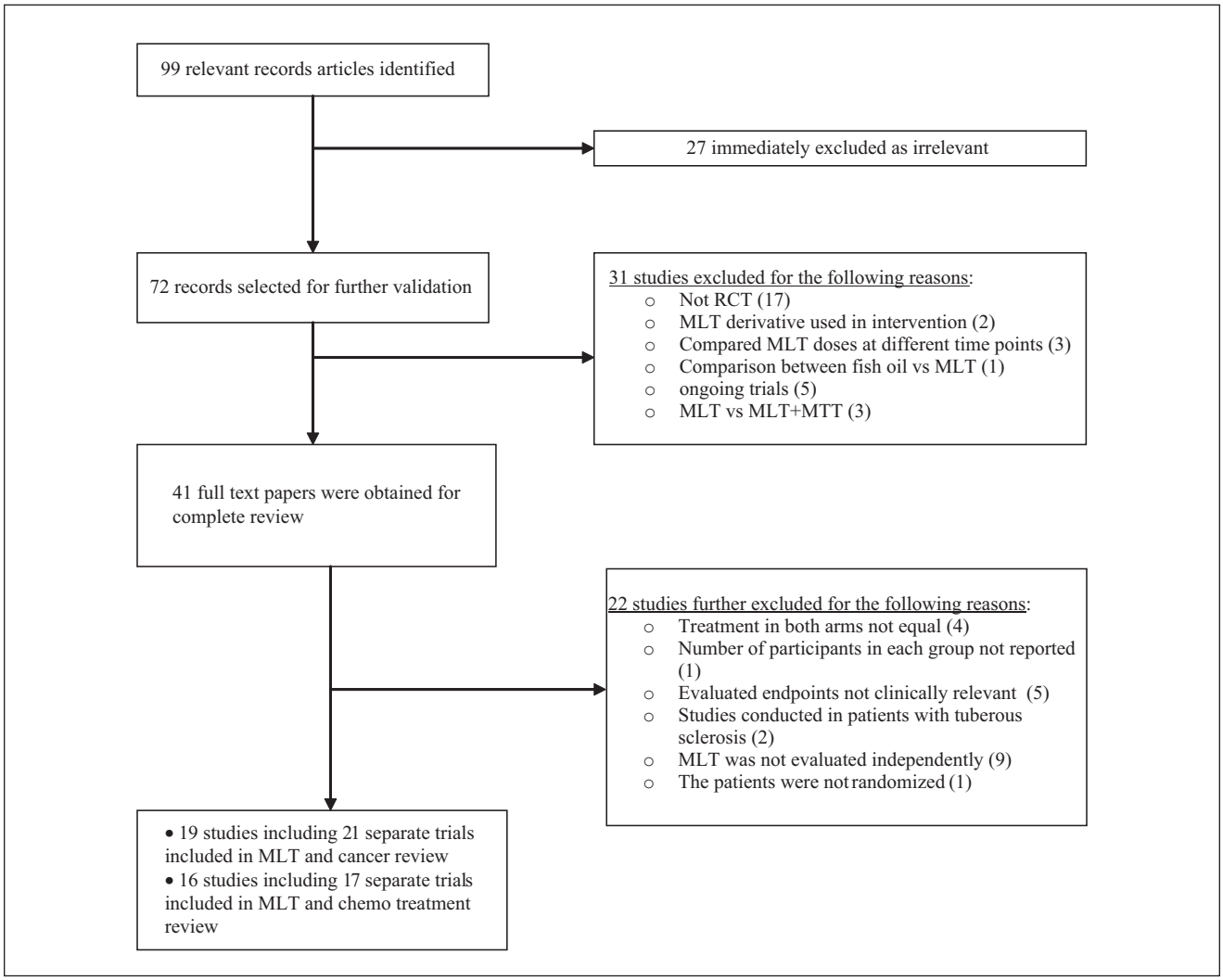

Figure 1. Flow diagram of studies assessed in the systematic review and meta-analysis
Abbreviations: MLT, melatonin; RCT, randomized controlled trial.

on MLT versus no MLT using the DerSimonian-Laird random-effects method.[15] This method recognizes and anchors studies as a sample of all potential studies and incorporates an additional between-study component to the estimate of variability. We calculated the I^2 statistic for each analysis as a measure of the proportion of the overall variation attributable to between-study heterogeneity.[16] Publication bias was tested using both the Egger test with the funnel plot and Kendall's test on standardized effect versus variance. Forest plots are displayed for the primary analysis, showing individual study effect measures with 95% CIs and the overall DerSimonian-Laird pooled estimate. StatsDirect was used for all meta-analytic procedures (StatsDirect, Copyright 1993–2004, Manchester).

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Results

Figure 1 details the yield of the source and the study selection. κ for initial decisions on inclusion in the study was 0.9 (95% CI = 0.6-1), suggesting excellent agreement.

Table 1. Characteristics of Included Studies

Author	N	Median Age (T/C)	Performance Status (Karnofsky Score)	Diagnosis and Staging	MLT dose (mg/d)	MLT Treatment Duration	Treatment Intervention Group	Treatment Control Group
Lissoni et al[32]	80	61/58	70	Metastatic solid tumor	20	Take with chemo till disease progression	Chemo + MLT CDDP + VP-16 MTX 5FU + FA	Chemo CDDP + VP-16 MTX 5FU + FA
Cerea et al[18]	30	66/63	90	Monastic colorectal cancer	20	Take with CPT-11 for 9 to 12 cycles	CPT-11 + MLT	CPT-11
Lissoni et al[24]	80	53/56	60	Advanced solid tumor	40	1 Week before IL-2 till disease progression or toxicity	IL-2 + MLT	IL-2
Lissoni et al[21]	63	61/59	70	Metastatic non–small cell lung cancer	10	Take with chemo till disease progression	MLT	Supportive care
Lissoni et al[30]	91	62/60	80	Advanced solid tumor	40	1 Week before IL-2; take with IL-2 for 147cycles (76 vs 71;T vs C)	IL-2 + MLT	IL-2
Lissoni et al[30]	25	54/56	90	Advanced solid tumor	40	1 Week before TNF; take with TNF for 65 cycles (34 vs 31;T vs C)	TNF + MLT	TNF
Lissoni et al[23]	250	61/59	80	Advanced solid tumor	20	1 Week before chemo till disease progression	Chemo + MLT CDDP + VP-16 CDDP + 5-FU MTX PTX GEM DOX 5FU + FA	Chemo CDDP + VP-16 CDDP + 5-FU MTX PTX GEM DOX 5FU + FA
Lissoni et al[31]	70	64/61	80	Non–small cell lung cancer	20	Take with chemo even during disease progression	Chemo + MLT CDDP + VP-16	Chemo CDDP + VP-16
Lissoni et al[28]	100	61/59	80	Non–small cell lung cancer	20	1 Week before chemo, take with it even during disease progression	Chemo + MLT CDDP + VP-16	Chemo CDDP + VP-16
Lissoni[19]	1440	66/65	60	Advanced, untreatable solid tumor	20	≥2 months	Support care + MLT	Supportive care
Lissoni[19]	200	60/61	100	Advanced solid tumor	20	1 Week before chemo till disease progression	Chemo + Support care + MLT NA	Chemo + Support care NA
Yan et al[34]	100	29-72	NA	Primary hepatocellular carcinoma	20	1 Week before chemo, take with it until 21 days after it	Chemo + MLT TACE	Chemo TACE
Lissoni et al[22]	50	56/58	70	Solid tumor with brain metastases	20	Take till the progression of brain metastasizes	Supportive care + MLT	Supportive care
Lissoni et al[27]	30	59/56	80	Malignant melanoma	20	Take it even during disease progression	Supportive care + MLT	Supportive care
Lissoni et al[29]	30	56/54	80	Metastatic renal cell cancer	20	1 Week before IL-2 till disease progression	IL-2 + morphine + MLT	IL-2 + morphine
Lissoni et al[35]	30	51/48	80	Brain glioblastomas	20	Take with radiotherapy till disease progression	Radiotherapy + MLT	Radiotherapy
Lissoni et al[25]	33	NA	NA	Metastatic renal cell cancer	10	5 Days before IL-2, take with IL-2 for 33 cycles	IL-2 + MLT	IL-2

(*continued*)

Table 1. (continued)

Author	N	Median Age (T/C)	Performance Status (Karnofsky Score)	Diagnosis and Staging	MLT dose (mg/d)	MLT Treatment Duration	Treatment Intervention Group	Treatment Control Group
Lissoni[20]	370	NA	NA	Metastatic solid tumor	20	1 Week before chemo till disease progression	Chemo + MLT CDDP + VP-16 CDDP + GEM OXA + 5-FU + FA + CPT-11 CDDP + Epi + 5-FU + FA	Chemo
Brackowski et al[17]	14	NA	NA	Metastatic solid tumor	40	1 Week prior to TNF and 1 week after TNF interruption	TNF + MLT	TNF
Lissoni and Barni[33]	40	65/66	70	Metastatic breast cancer	20	Take with TMX	TMX + MLT	TMX
Lissoni et al[26]	571	67/66	80	Metastatic solid tumor	20	Take it even during disease progression	Supportive care + MLT	Supportive care

Abbreviations: Chemo, Chemotherapy; CDDP, cisplatin; IL, interleukin; TNF, tumor necrosis factor; MLT, melatonin; VP-16, etoposide; GEM, gemcitabine; OXA, oxaliplatin; 5-FU, 5-fluorouracil; FA, folates; CPT-11, irinotecan; MTX, Mitoxantrone; CBDCA, Carboplatin; PTX, Paclitaxel; Epi, epirubicin; TACE, chemoembolization; TMX, tamoxifen; NA, no detail mentioned.

A total of 19 studies[17-35] consisting of 21 separate clinical trials were included in the systematic review of MLT and all cancer treatments. In one of these studies,[19] there were 2 separate trials—one that explored chemotherapy with and without MLT and another that explored supportive care with and without MLT. One other paper[30] also included 2 separate trials, both of which explored chemotherapy with and without MLT. In the MLT treatment groups, all participants were provided single oral doses of MLT in the evening (10 mg in 1 study, 20 mg in 16 studies, and 40 mg in the remaining study). There was no provision of any level of MLT to participants in the control groups. See Table 1 for further details of each of the individual studies.

All studies were published between 1992 and February 2010 and included 3697 patients with metastatic, solid tumor cancers. Studies included a wide variety of biologically and clinically distinct cancer cell types, including breast, colorectal, lung, and renal cell cancers; primary hepatocellular carcinoma; glioblastomas; and others. Most studies were conducted in patients with advanced or metastatic disease. Baseline participant Karnofsky scores ranged from 60 to 100. Most studies were small in sample size (median n = 70; range = 14 to 1440). All trials were written in English. One study was conducted in China, and all the other studies were conducted in either Italy or Poland by the same group of investigators.

Determinations of study quality according to each publication indicate that the quality was low overall. Table 2 provides details on study methodology for each trial, including quality criteria that contribute to a risk of bias. There is no real description of either randomization or allocation concealment in any of the publications; however, following communication with the authors, it was reported that randomization and allocation concealment were well adhered to. The same situation applied with regard to ethics approvals and the provision of informed consent by the patient. Intention to treat and stratification were well reported in the studies. Two studies reported sample size calculations prior to the trial, and all the studies were open labeled, with neither patients nor assessors being blinded.

The pooled RRs demonstrated that 1-year mortality was 0.63 (95% CI = 0.53-0.74; $P \leq .001$; $I^2 = 78\%$). Complete response, partial response, and stable disease were all significantly improved from the addition of MLT. Using a random-effects model, the results are 2.33 (95% CI = 1.29-4.20), 1.90 (95% CI = 1.43-2.51), and 1.51 (95% CI = 1.08-2.12), respectively. Eggers test using a funnel plot found no evidence for publication bias.

With respect to an exploration of side effects and symptoms caused either by the cancer itself or cancer treatment apart from chemotherapy, MLT was found to significantly reduce occurrences of alopecia, anemia, asthenia, and thrombocytopenia. Adjuvant MLT was also found to significantly reduce the occurrence of alopecia, anemia, asthenia, and thrombocytopenia. The pooled RR was 0.86 (95% CI = 0.75-0.97), 0.83 (0.71-0.97), 0.44 (0.39-0.50), and 0.21 (0.15-0.30) for these outcomes, respectively. Eggers test found some evidence for publication bias for anemia

Table 2. Reporting of Trial Methodology Contributing to Quality and Risk of Bias

Author	Detail of Randomization	Allocation Concealment	Consent Statement	Ethics Review	Sample Size	ITT	Withdraw	Adverse Effect	Flow Diagram	Stratification	Blinding
Lissoni et al[32]	N	N	Y	N	N	Y	N	Y	N	Y	N
Cerea et al[18]	N	N	Y	N	N	Y	Y	Y	N	N	N
Lissoni et al[24]	N	N	Y	N	N	Y	N	Y	N	N	N
Lissoni et al[21]	N	N	Y	N	N	Y	N	N	N	Y	N
Lissoni et al[30]	N	N	Y	N	N	Y	N	Y	N	N	N
Lissoni et al[23]	Y	N	Y	N	Y	Y	Y	Y	Y	Y	N
Lissoni et al[31]	N	N	Y	N	N	Y	N	Y	N	Y	N
Lissoni et al[28]	N	N	Y	N	N	Y	N	Y	N	Y	N
Lissoni[19]	N	N	Y	N	N	Y	N	Y	N	Y	N
Yan et al[34]	N	N	N	N	N	Y	N	N	N	Y	N
Lissoni et al[22]	N	N	N	N	N	N	N	Y	N	Y	N
Lissoni et al[27]	N	N	Y	N	N	Y	N	Y	N	Y	N
Lissoni et al[29]	N	N	Y	N	N	Y	N	Y	N	Y	N
Lissoni et al[35]	N	N	Y	N	Y	Y	N	Y	N	Y	N
Lissoni et al[25]	N	N	N	N	N	Y	N	Y	N	N	N
Lissoni[20]	N	N	Y	N	N	Y	N	Y	N	Y	N
Brackowski et al[17]	N	N	Y	N	N	N	N	Y	N	N	N
Lissoni and Barni[33]	N	N	Y	N	N	Y	N	Y	N	Y	N
Lissoni et al[26]	N	N	Y	N	N	Y	N	Y	N	Y	N

Abbreviations: Y, yes; N, no; ITT, intention to treat.

(−0.46, $P < .05$), asthenia (−0.84, $P < .05$), and thrombocytopenia (−0.68, $P < .05$).

In the trials that tested the combination of MLT with chemotherapy, it was also found that MLT reduced mortality at 1 year and improved complete response, partial response, and stable disease. Using a random-effects model, the pooled RRs were 0.60 (95% CI = 0.54-0.67),1.93 (1.49-2.49), 2.53 (1.36-4.71), 1.70 (1.37-2.12), and 1.15 (1.00-1.33), respectively. I^2 demonstrated heterogeneity for 1-year mortality (59.8%), and Eggers test demonstrated evidence of publication bias (2.12, $P < .05$).

Regarding results for chemotherapy-associated toxicities, all trials in which chemotherapy was included as treatment were reviewed for the incidence of toxicity-induced comorbidities. Consistent outcomes amenable to meta-analysis included asthenia, leucopenia, nausea and vomiting, hypotension, and thrombocytopenia. The pooled RR for these outcomes that demonstrated benefit are 0.45 (95% CI = 0.38-0.53), 0.65 (0.43-0.97), 0.84 (0.72-0.97), 0.21 (0.10-0.47), and 0.17 (0.11-0.27), respectively. Side effects of therapy or symptoms caused by the cancer that were not improved by the addition of MLT included alopecia, anemia, and diarrhea. The I^2 showed no heterogeneity in the trials.

Table 3 provides further detail for all outcomes and tests for heterogeneity in trials in which chemotherapy was used. Figure 2 provides Forest plots for some of the major outcomes analyzed according to whether or not chemotherapy was used in the trials.

Discussion

Important Findings

This meta-analysis shows a significant positive effect for cancer patients with the use of oral MLT, alone and in combination with chemotherapy. Benefits were seen on survival rates, treatment response rates, and disease progression and on the toxicity profile of a number of chemotherapy agents. It is important to note that these benefits were observed despite the fact that the analysis combined a wide variety of biologically and clinically distinct cancer types, across which MLT nonetheless demonstrated similar results. The large effect sizes and good safety profile of this intervention lends a strong degree of clinical significance to these findings. This meta-analysis is the first to examine specifically the effect of MLT on toxicity associated with chemotherapy and radiation therapy. In addition, this analysis confirms earlier findings of Mills et al[4] indicating increased 1-year survival in patients with active cancer who receive MLT.

Strengths/Limitations

The methodological strengths of the systematic review include the breadth of the initial search, which encompassed 7 databases, data extraction completed in duplicate, and a qualitative analysis of the included studies. In addition, we undertook communication with trial investigators

Table 3. Outcomes as Assessed in All Trials and in Only Those Trials Where Melatonin Was Used as an Adjuvant to Chemotherapy[a]

	Number of Trials	RR	CI (lower)	CI (higher)	I^2 (inconsistency)	Kendall's τ	Egger Test
Outcomes in all studies							
One-year survival in all studies	13[19-24,27,29,31,33-35]	0.63	1.82	3.46	77.1%	0.56	1.87
Complete response	12[18-21,23,24,26,28,29,31-33]	2.33	1.29	4.20	0	–0.85*	–0.48
Partial response	16[18-21,23,24,26,28-33,35]	1.90	1.43	2.51	28%	0.27	1.12
Stable disease	12[18-21,23,24,26,28,29,31,33]	1.51	1.08	2.12	83.9%	0.30	–0.10
Alopecia	6[19,23,28,31,32,35]	0.86	0.75	0.97	0	–0.47(low power)	–0.44
Anemia	10[17-19,23-25,28,31,32]	0.83	0.71	0.97	0	–0.64**(low power)	–0.46**
Asthenia	13[17-20,23-25,28,30-32]	0.44	0.39	0.50	0	–0.18	–0.84**
Thrombocytopenia	11[17,19,20,23,25,28,30-32]	0.21	0.15	0.30	0	0.09	–0.68**
Outcomes in studies with chemotherapy							
One-year mortality	8[19,20,23,24,29,31,33,34]	0.60	0.54	0.67	59.8%	0.64 (low power)	2.12**
Complete response	10[18-20,23,24,28,29,31-33]	2.53	1.36	4.71	0	–0.68	–0.22
Partial response	12[18-20,23,24,28-33]	1.70	1.37	2.12	2.5	0.36	0.94
Stable disease	9[18-20,23,24,28-33]	1.15	1.00	1.33	0	–0.05 (low power)	–0.21
Alopecia	5[19,23,28,31,32]	0.87	0.76	1.01	0	–0.8 (low power)	–0.4
Anemia	9[17-19,23-25,28,31,32]	0.71	0.47	1.07	0	–0.67**(low power)	–0.75**
Asthenia	12[17-20,23-25,28,30-32]	0.45	0.38	0.53	0	–0.15	–1.13**
Cardiac symptoms	2[17,25]	1.03	0.16	6.65	—	—	—
Diarrhea	8[17-19,23-25,31,32]	0.74	0.54	1.00	0	0.27 (low power)	–0.05
Fever	3[17,24,25]	0.63	0.19	2.08	—	—	—
Leucopenia	5[18,19,23,31,32]	0.65	0.43	0.97	0	0.2 (low power)	–0.70
Nausea, vomiting	6[18,19,23,24,31,32]	0.84	0.72	0.97	0	–0.52 (low power)	–0.32
Thrombocytopenia	10[17,19,20,23,25,28,30-32]	0.17	0.11	0.27	0	0.11**(low power)	–0.31
Hypotension	4[17,25,30]	0.21	0.10	0.47	15.1%	1	2.73**

Abbreviations: RR, risk ratio; CI, confidence interval.
[a]The dashes refer to cases with too few strata to conduct a robust evaluation. *$P < .001$; **$P < .05$.

to clarify ambiguous methodologies. The meta-analysis is less likely to reflect risk of bias caused by inclusion of randomized controlled trials only. Addressing the issue of potential interactions with conventional therapy is important for the clinical application of our findings.

The limitations of this work include the fact that the majority of the trials were conducted by the same group of investigators in Italy and Poland (Lissoni and colleagues). Although this in itself is not sufficient grounds for an inference of bias, it is grounds at least for further investigation. Externally conducted trials of MLT in the area of cancer therapy are sorely needed, and there are a handful of trials under way presently that will address this. A joint project with the Ottawa Hospital is currently enrolling participants in a large, randomized, multicenter, placebo-controlled study investigating the effects of supplemental MLT in lung cancer patients. A similar trial investigating the efficacy of MLT in reducing the side effects of chemotherapy in patients with stage III and IV non–small cell lung cancer is under way at the Cancer Treatment Centers of America. The National Cancer Institute also lists several trials under way at the MD Anderson Cancer Center and elsewhere investigating the effect of MLT on cancer-related anorexia/cachexia and on fatigue in cancer patients. When published, these studies will lend further objectivity and a clinical evidence base to the larger totality of evidence surrounding the use of MLT for cancer treatment.

Several of the studies included in this analysis failed to report blinding, randomization, allocation concealment, informed consent, and ethics approval. However, direct communication with study investigators indicated that with the exception of blinding, these were all enforced, and standard methods of enrollment, sequence generation, and analysis were used in the implementation of the trials, raising the level of quality of the studies included. None of the studies analyzed were blinded, which does increase the risk of bias.

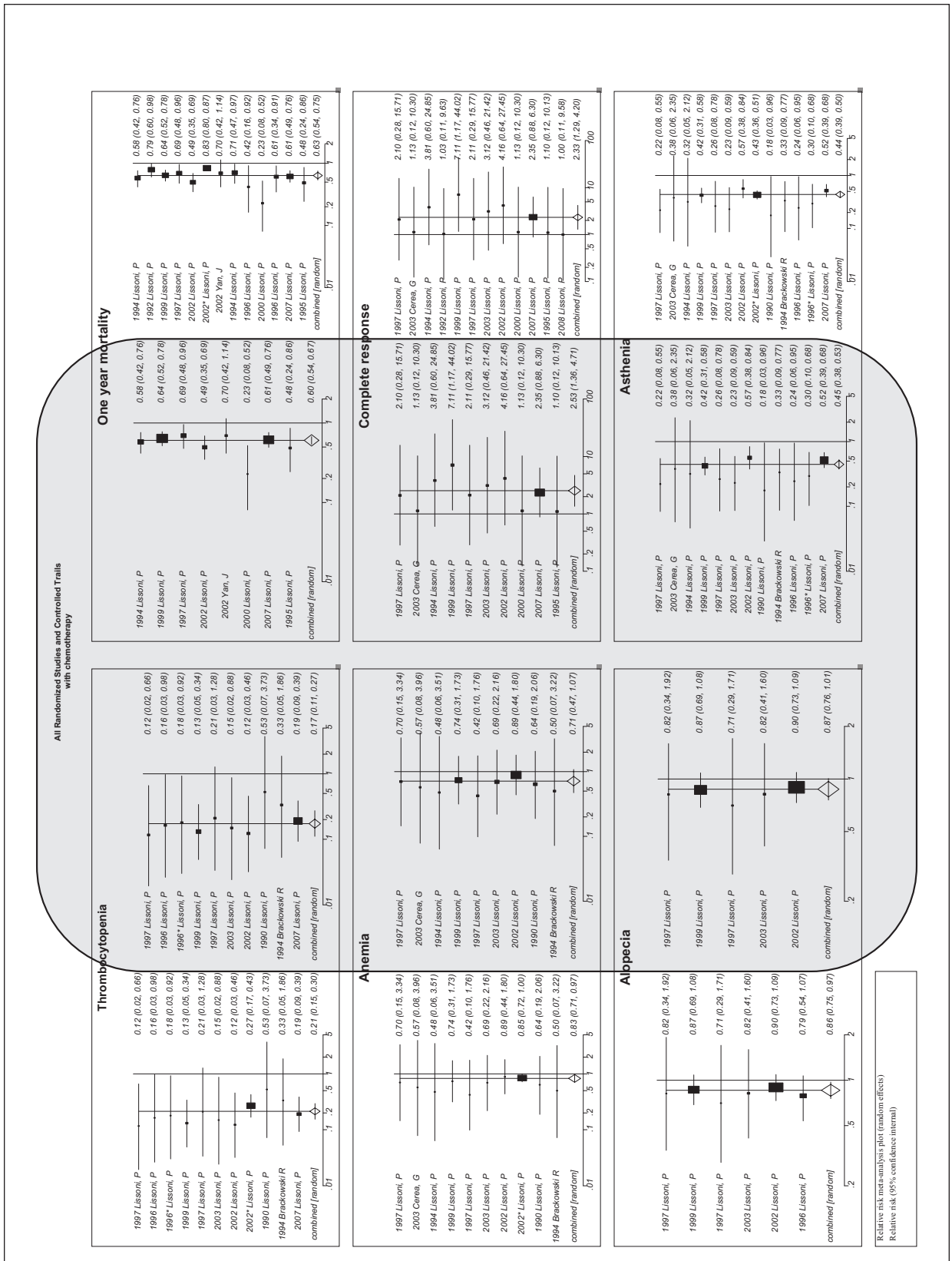

Figure 2. Meta-analysis of the effect of melatonin on cancer treatment outcomes: Relative risk associated with chemotherapy, with and without melatonin

Contextualizing the Evidence

The findings of this study are consistent with the melatonin hypothesis and the observational evidence on which it is based, both of which implicate disrupted MLT secretion or possible deficiency as a causal factor in carcinogenesis.[9]

Srinivasan et al[3] have published a thorough review describing the possible mechanisms by which MLT may exert its anticancer effects. MLT modulates estrogen and androgen activity, acts as an immunomodulator, inhibits cancer cell growth and proliferation, inhibits angiogenesis while protecting precursors of hematopoesis, and scavenges free radicals.[3] MLT modulates estrogen through its SERM and SEEM activity[3,13] and inhibits the growth of androgen-sensitive prostate cancer cells.[3] In certain cancer cell types, MLT inhibits the uptake of linoleic acid, which prevents the formation of its mitogenic metabolite and inhibits the formation of the proangiogenic factor, endothelin-1. In addition, MLT possesses radioprotective effects and scavenges free radicals in part through its stimulation of glutathione production.[3] MLT may exert direct apoptotic effects by blocking cell cycle progression from the G phase to the S phase and by increasing p53 and p21 gene expression.[3]

With respect to immunopotentiating effects, MLT increases immunosurveillance by stimulation of lymphocyte, monocyte/macrophage, and natural killer cell activity. Human lymphoid cells also synthesize MLT, which regulates the immune system in a paracrine and autocrine manner, and MLT has been shown to enhance the production of cytokines IL-1, IL-2, IL-6, IL-12, IFN-γ, and TNF-α.[3]

With the exception of free-radical scavenging, these activities are thought to be receptor mediated through receptors MLT1 and MLT2.[3] Nuclear binding sites for MLT have been identified in most tissue types, and it is thought that MLT may affect genomic activity at these sites, which include receptors belonging to the retinoic acid receptor family.[2,3]

Safety and Pharmacokinetics

MLT appears to have a high safety profile, based on human trials and reported use. Although the doses used in the studies reviewed here are significantly higher (10-50 mg/d) than those used for other indications (0.5-5.0 mg/d), none of these studies found any serious side effects related to MLT; on the contrary, MLT decreased some of the side effects resulting from chemotherapy and radiation therapy.

MLT is lipid soluble and diffuses easily across all membranes, making it highly available throughout the body.[36] However, it is cleared rapidly, with a relatively short half-life of between 30 and 57 minutes. It should be noted that 90% of MLT is cleared in a single passage through the liver by cytochrome P450 enzymes: CYP1A2, CYP1A1, and CYP1B1.[2,3] In the liver, MLT is metabolized to 6-hydroxymelatonin, conjugated to a sulfate or glucuronide, and excreted in the urine. Small amounts of unmetabolized MLT may be excreted in bile, and some may be excreted directly through urine.[2] In addition to the rapid hepatic metabolism of MLT, it may also be metabolized nonenzymatically in all the body's cells.[3]

Buscemi et al[37] have published a meta-analysis investigating the safety and efficacy of MLT for insomnia. Although the dosages examined in their study are considerably lower than those reviewed here, the results add further support to our findings, which suggest a high safety profile for MLT.

Future Directions of Research

Further study of MLT as an adjunctive treatment for cancer conducted by independent researchers is needed to support the findings in this meta-analysis. In addition, the level of observational evidence on dysregulated MLT rhythms increasing cancer risk invites further study into the chemopreventive potential of exogenous MLT in a clinical setting.

We conclude that MLT may safely increase 1-year survival and response rates when added to many forms of standard cancer care and may also alleviate the toxicity related to chemotherapy and improve cancer-related symptoms as well. Independently conducted well-designed trials are needed to confirm these findings.

Author's Note

DS, EM, and AS were responsible for the study concept and design; PW, DS, TT, and DAK were responsible for the collection and assembly of data; PW, DAK, EM, and DS were responsible for data analysis and interpretation; PW, DS, TT, AS, and HF drafted the manuscript; DS supervised the study; all authors participated in the analysis and interpretation of data and critical revision of the manuscript.

Declaration of Conflicting Interests

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