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Comparative clinical benefits of systemic adjuvant therapy for paradigm solid tumors

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ABSTRACT

Adjuvant therapy employing cytotoxic chemotherapy, molecularly targeted agents, immunologic, and hormonal agents has shown a significant impact upon a variety of solid tumors. The principles that guide adjuvant therapy differ among various tumor types and specific modalities, but generally indicate a greater impact of therapy in the postsurgical setting of micrometastatic disease, for which adjuvant therapy is commonly pursued, vs. the setting of gross unresectable disease. This review of adjuvant therapies in current use for five major solid tumors highlights the rationale for current effective adjuvant therapy, and draws comparisons between the adjuvant regimens that have found application in solid tumors.

Introduction

The aim of systemic adjuvant therapy following tumor resection is to reduce the risk of disease recurrence and distant metastasis, thereby improving survival. Recurrence risks after resection generally increase with the extent of invasion of primary tumor and degree of regional lymph node involvement. In solid tumors, adjuvant therapy ranges from chemotherapy that has shown benefit in advanced disease to more specific application of hormonal, immune, and molecularly targeted therapies. Adjuvant use of these agents is based upon increased understanding of tumor biology and progression pathways, as well as an understanding of the processes that accompany progression (e.g., immunomodulation). In colon cancer, recent trials suggest that we cannot always extrapolate outcomes in advanced disease to the adjuvant setting, particularly with targeted therapies, and that new paradigms are needed to identify agents that should be considered for use in the adjuvant setting. This overview of the current status of adjuvant therapy for a number of paradigmatic solid tumors compares and contrasts the progress that has been made in the different disease areas. Non-small-cell lung cancer (NSCLC), colorectal cancer, sarcoma, melanoma, and breast cancer were selected for this review as leading solid tumors that represent the major incident and rising tumors, as well as tumors for which the use of adjuvant therapy has been established in cooperative group studies. Information sources searched were online libraries (PubMed/Medline) and recognized national/international treatment guidelines.

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Current status of adjuvant therapy in major solid tumors

The current adjuvant therapies applicable for the major solid tumors reviewed here are summarized in Table 1.

In non-small-cell lung cancer (NSCLC), adjuvant chemotherapy is currently considered following resection of stage II–III disease and in high-risk, margin-negative, stage IB disease (Table 1).[1] Cisplatin-based chemotherapy doublets are the mainstay of adjuvant therapy. Various doses and regimens are used but commonly 4 cycles of 21 or 28 days are given. There is no specific recommendation to treat based on histologic subtype. However, in the treatment of metastatic NSCLC, a subgroup analysis of squamous cell histology demonstrated inferior survival in the cisplatin and pemetrexed arm.[2] It is unclear if this can be extrapolated to the adjuvant setting.

Chemotherapy based on 5-fluorouracil (5FU) is the standard adjuvant therapy for resected stage III colorectal cancer; its relative contribution in stage II disease remains controversial. National Comprehensive Cancer Network (NCCN) guidelines[3] recommend 6 months of adjuvant chemotherapy with combinations of 5FU/leucovorin [LV]/oxaliplatin (FOLFOX; FLOX), capecitabine/oxaliplatin (XELOX; CapeOx), capecitabine alone, or 5FU/LV alone, in stage III disease and in high/intermediate-risk stage II patients, based on clinicopathologic risk factors after discussion of the risks and benefits with the patient (Table 1). If oxaliplatin is not appropriate, 5FU/LV may be used. Observation, 5FU/LV, capecitabine, or a clinical trial is recommended for stage II disease without high-risk features.

Sarcomas are a biologically complex group of mesenchymal tumors. Chemotherapy using anthracyclines and alkylating agents is currently the standard adjuvant approach for osteosarcoma, Ewing's sarcoma, and soft tissue sarcomas (STS). Adjuvant chemotherapy is accepted for the treatment of localized, high-grade osteosarcoma and is recommended in low grade or periosteal sarcoma with high-grade pathology.[4] The currently recommended combination chemotherapy regimens are summarized in Table 1. In Ewing's sarcoma, the high rates of relapse after local therapy suggest that micrometastatic disease should be considered present at diagnosis.[5–7] Therefore, adjuvant therapy with cyclophosphamide, doxorubicin, vincristine, ifosfamide and etoposide combinations is recommended in all patients (Table 1).[4] In STS, adjuvant chemotherapy has resulted in small but consistent benefits. Adjuvant doxorubicin in combination with other chemotherapy agents is accepted (Table 1). NCCN guidelines suggest anthracycline-based adjuvant chemotherapy in high-risk patients with good performance status.[8] However, the use of adjuvant chemotherapy in STS remains controversial and is therefore subject to regional and individual practice patterns; patient selection is paramount. It should be restricted to patients with high-risk stage II and III disease at presentation, identified on the basis of clinicopathologic features, namely those with large (>5 cm), high-grade extremity tumors, excellent performance status, and no comorbidities that would increase their risk of cardiac and/or renal failure associated with doxorubicin and ifosfamide. For truncal or retroperitoneal sarcomas the evidence is less supportive, and treatment should be considered on a case-by-case basis.

Table 1
Current adjuvant systemic therapy for five major solid tumors.

Tumor	Adjuvant therapy	Selection factor	Proportion of patients eligible
NSCLC[1]	Cisplatin-based chemotherapy doublets[a]	High-risk margin-negative stage IB Stage II-III	<37%[b]
	Carboplatin and paclitaxel	Patients as above not able to tolerate cisplatin	–
Colon cancer[3]	FOLFOX or FLOX or XELOX (CapeOx)	High or intermediate risk stage II[c] Stage III	21%[d]
	5FU/LV Capecitabine alone	As above if oxaliplatin not appropriate	–
	Observation, 5FU/LV, capecitabine, or clinical trial	Stage II without high-risk features	-
Osteosarcoma[4]	Cisplatin and doxorubicin ± high dose methotrexate ± ifosfamide Ifosfamide + etoposide (IE) Ifosfamide + cisplatin + epirubicin	High-grade disease Low-grade disease with high-grade pathology	>90%
Ewing's sarcoma[4]	Vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide combination	All patients	100%
Soft tissue sarcoma[8]	Doxorubicin-based CT[e] Epirubicin and ifosfamide	Stage II–III	50–60%
Melanoma	IFN-α (high and intermediate dose) or PEG-IFN-α2b	Stage IIB–III Stage IIIA/N1	<92%[b]
Breast cancer[15,18]	Endocrine therapy (tamoxifen, aromatase inhibitors)	Stage I–III disease ER and/or PR-positive disease	60–70%
	Anti-HER2 therapy	Stage I-III disease HER2/neu overexpressing disease	15–20%
	Chemotherapy (doublets or triplets)[f] Anthracycline/cyclophosphamide doublet with sequential taxane	Stage I–III Selection based upon recurrence risk, age, comorbidities, and other factors	60–70%

ER, estrogen receptor; FLOX/FOLFOX, 5FU/LV/oxaliplatin; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; XELOX (CapeOx), capecitabine/oxaliplatin.

[a] Cisplatin plus vinorelbine or etoposide or vinblastine or gemcitabine or docetaxel.

[b] Estimates based on SEER Cancer Statistics Review (1975–2008) data for localized and regional disease at diagnosis (includes patients with very early stage disease who would not be suitable for adjuvant therapy).

[c] T4 tumors (IIB or IIC), grade 3 or 4, lymphovascular or perineural invasion, bowel obstruction, localized perforation or close/indeterminate/positive margins, inadequately sampled nodes.

[d] Estimated from the American Joint Committee on Cancer 7th edition (page 154).

[e] Combination agents include ifosfamide, dacarbazine and mesna.

[f] Examples of commonly used doublets include TC (docataxel, cyclophosphamide) and AC (doxorubicin, cyclophosphamide), and triplets include CMF (cyclophosphamide, methotrexate, and 5FU), FEC (5FU, epirubin, cyclophosphamide), and TAC (docetaxel, doxorubicin, and cyclophosphamide).