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Short Review

The Role of Antitumor Antibiotics in Current Oncologic Practice

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Summary. *The antitumor antibiotics have thus made a major impact on oncologic practice. The continued search for productive strains of these organisms should be encouraged; in addition, the activity and toxicity spectrum suggests the need for vigorous analogue development. An active anthracycline devoid of cardiotoxicity, a bleomycin with no effect on pulmonary tissue, an analogue of streptozoticin devoid of nephrotoxicity — these would be advances of inestimable benefit to the cancer patient of the future.*

Introduction

The antitumor antibiotics are a heterogeneous group of antineoplastic agents which share a common origin as fermentation products of microbial cultures. This brief review of selected agents will emphasize those agents that play a major role in current oncologic practice in the USA. We are indebted to our Japanese colleagues for their vital role in the preclinical and clinical development of several of the agents in widespread use today. In the course of this discussion we will present specific points to aid in future development in this important area. Table 1 lists the agents to be described and the areas where they have exhibited a major impact in clinical practice.

Mechanism of Action

The mechanisms of action of the antitumor antibiotics are varied. The actinomycins, mithramycin and chromomycin A_3, bind to DNA and inhibit DNA-dependent RNA synthesis [82, 43, 89, 39], while the anthracycline antibiotics, daunomycin and adriamycin, intercalate between base pairs and inhibit RNA and DNA synthesis [12].

Bleomycin is a peptide which reacts with DNA and uses strand scission [78] while alkylation is the predominant mode of action of streptonigrin, mitomycin C, and porfiromycin [15, 79]. Streptozoticin has a complex mechanism of action that may include alkylation [66]. The common feature in the mechanisms of action of the antitumor antibiotics seems to be their interaction with DNA. All of these drugs are also relatively noncycle specific.

Table 1. Antitumor antibiotics and their major impact in oncologic practice

Drug	Disease — major impact
Actinomycin D	Trophoblastic disease, germinal tumors of testis and ovary, childhood tumors, Ewing's sarcoma, Kaposi's sarcoma
Mithramycin	Hypercalcemia of malignancy, testicular tumors
Chromomycin A_3	—
Daunomycin	Acute myelogenous leukemia
Adriamycin	Acute myelogenous leukemia, lymphomas, sarcomas, breast cancer
Bleomycin	Testicular, malignant lymphomas
Streptonigrin	—
Mitomycin C	—
Porfiromycin	—
Streptozoticin	Islet cell tumors

Toxicity

The human toxicology of the antitumor agents is of interest because of the unusual spectrum of toxicities both acute and chronic.

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Acute Toxicities. Myelosuppression is the principal dose limiting toxicity of actinomycin D, daunomycin, and adriamycin. It is rather easily handled by dose and schedule modifications. Cumulative myelosuppression is not a serious clinical problem [25, 87, 7]. However, acute and chronic myelosuppression are a serious problem with streptonigrin, mitomycin C, and porfiromycin, and seriously limit the utility of these agents [56, 52].

Chromomycin A_3, bleomycin, and streptozoticin are infrequently myelosuppressive when used alone unless there has been extensive prior chemotherapy or radiation [44, 8, 72]. The toxicity of mithramycin is global even though leucopenia is infrequent. Life-threatening thrombocytopenia, hepatitis with coagulation defects, cutaneous vasculitis, and renal failure are seen with conventional dosages [40]. Alternate day schedules of drug administration have been studied in a few patients and are considerably less toxic [41].

Renal toxicity is clearly the major dose-limiting toxicity for chromomycin A_3 and streptozoticin but may be modified by appropriate dosing and scheduling [67, 11].

The metabolic effects of actinomycin D and mithramycin are of considerable interest. Hypocalcemia is frequent with mithramycin therapy [40]. In fact, the major current clinical indication for mithramycin therapy is hypercalcemia [57, 74]. Both actinomycin D [76] and mithramycin [68] are effective in temporary reversal of the metabolic abnormalities and symptomatology of Paget's disease of bone and are under active investigation in this nonmalignant disease.

Streptozoticin is uniquely toxic to the pancreatic islets of Langerhans [38]. This toxicity has been exploited by the use of streptozoticin in islet cell neoplasms [11]. Bleomycin regularly causes fever after administration and anaphylactoid reactions occur in about 1% of patients treated [8, 9].

Cumulative Toxicities. Major cumulative dose-related toxicities remain an unsolved problem in the clinical use of bleomycin and the anthracycline antibiotics, adriamycin and daunomycin. Bleomycin induces interstitial pulmonary lesions which may be progressive and fatal, although most early abnormalities regress with cessation of the drug [9]. This has limited the cumulative dose of the drug that can be given and bleomycin therapy is of necessity relatively short-term [8].

Adriamycin and daunomycin produce electrocardiographic changes in 20–30% of patients receiving the drugs [88]. These EKG changes are usually reversible and are generally not a reason to discontinue therapy. A frequently fatal diffuse cardiomyopathy is the major cumulative toxicity of these agents and has led to guidelines for a maximum total permissible dose [88, 47]. The cardiotoxic threshold dose for adriamycin is unknown, as histologic abnormalities have been noted by cardiac biopsy in patients receiving as little as 200 mg/m^2 [6]. Efforts to predict for the future development of cardiomyopathy by noninvasive measures have been unproductive. Study of systolic time intervals and echocardiographic techniques have demonstrated abnormalities of progressive severity related to total dose [47, 6], but have not successfully predicted the onset of congestive failure in all cases. Fatal cardiomyopathy occasionally ensues weeks or months after cessation of therapy even when the studies were normal at termination of therapy [86, 47]. Symptomatic clinically detectable cardiomyopathy is rare at cumulative doses under 550 mg/m^2 of adriamycin and rises precipitously thereafter [46]. Daunomycin has been associated with a cardiomyopathy at a threshold dose of 600 mg/m^2 with a rapid rise in incidence above this level [86].

The limitations of total dosage may have another serious consequence, that of discontinuing an effective drug in a responding or stable patient, and resultant disease progression. For example, in a study currently in progress by the authors, 200 of 3500 patients had adriamycin discontinued because the maximum allowable dose had been reached. Of these patients, 25% were in complete remission, 20% in partial remission, and 25% were stable. Thus the fear of cardiotoxicity may have resulted in premature disease progression and overall reduction in survival.

Cardiotoxicity, including fear of cardiotoxicity, therefore remains a major problem of therapy with the anthracyclines. Currently this toxicity is minimized only by dose limitation although there have been suggestions that small weekly doses of adriamycin are less toxic [88]. Active investigation of less cardiotoxic analogues is under way, and rubidazone (NSC 164011), less toxic in the rat model, is under early clinical investigation [90].

Although none of the other antitumor antibiotics have exhibited cardiotoxicity, there is one report of an adriamycin-induced cardiomyopathy that seemed to be exacerbated by actinomycin D and mithramycin [45].

In summary, the antitumor antibiotics present a wide range of toxicities which challenge the supportive facilities of the oncologist. It would seem logical to continue the search for analogues that minimize cumulative myelosuppression, cardiac damage, and pulmonary toxicity as a high priority for future developments in this highly active group of agents.

Overall Antitumor Activity of the Antibiotics

Table 2 outlines the general activity of these agents, grouped according to a general disease classification.

Table 2. General activity of the antitumor antibiotics

Disease	Actinomycin D	Mithramycin	Chromomycin A_3	Daunomycin	Adriamycin	Bleomycin	Streptonigrin	Mitomycin C	Porfiromycin	Streptozoticin
Acute leukemia	NE	NE	–	#[a]	#[a]	NE	NE	NE	NE	NE
Lymphomas	#	NE	NE	NE	#	#	#[b]	#	NE	#
Childhood solid tumors	#[c]	NE	NE	NE	#[c]	NE	NE	NE	NE	NE
Bone sarcomas	#[c]	+	NE	NE	#[c]	NE	NE	+	NE	NE
Soft tissue sarcomas	#	NE	NE	NE	#	NE	NE	NE	–	+
Kaposi's sarcoma	#	NE	NE	NE	NE	#	NE	NE	NE	NE
Melanoma	#	+	NE	NE	–	NE	NE	+	NE	+
Breast cancer	+	+	+	NE	#	NE	+	#	NE	+
Squamous head and neck, cervix, esophagus	NE	NE	NE	NE	#	#	+	#	#	NE
Gastrointestinal adenocarcinoma	NE	+	+	+	#	NE[g]	NE	#	#	+
Endocrine (thyroid, adrenal, islet cell, carcinoid)	NE	NE	NE	NE	#[d]	NE	NE	NE	NE	#[e]
GU (kidnay, bladder, prostate)	NE	NE	NE	NE	#	NE	NE	#	NE	NE
GYN (ovary, uterus)	#	NE	NE	NE	#	NE	NE	NE	#	NE
Germ cell (ovary and testis)	#[f]	#[f]	NE	NE	+	#	NE	NE	NE	NE
Trophoblastic disease	#[f]	NE	NE	NE	NE	NE	NE	NE	NE	NE
Small cell lung	NE	NE	NE	NE	#	–	NE	+	NE	NE
Non small cell lung	–	+	NE	+	#	#	NE	+	NE	NE

[a] Major impact in acute myelogenous leukemia
[b] In clinical trial in one group (cancer and leukemia group B, CALGB)
[c] Potentially curative in combined modality treatment
[d] Active in thyroid and carcinoma
[e] Islet cell carcinoma
[f] May be curative alone or combined with other drugs
[g] Negative in colon cancer

= definite activity
+ = hints of activity
– = not active
NE = not evaluable

The evaluation of activity is based on extensive data, both published and unpublished, on file in the Investigational Drug Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment. An agent is designated '#' if it had definite clinical activity alone or in combination with other agents. In some programs cure may be possible. An agent is designated '+' if any responses were seen ('hints of activity'). The symbol '–' indicates no activity in at least 14 evaluable patients of the disease type. 'NE' is used when the compound has not been tested in at least 14 patients, and includes studies deemed unevaluable for a variety of reasons.

The discussion to follow will emphasize those agents which are currently accepted as major therapeutic advances in selected tumor types. No attempt will be made to cover all investigational applications unless there are implications for the immediate future.

Acute Leukemia

The major accomplishment of therapy with daunomycin or adriamycin has been in acute nonlymphocytic leukemia (ANLL). The role of these agents in acute lymphocytic leukemia has been limited because of the proven value of other agents [30]. Studies incorporating these agents have focused on reinduction of remission or treatment of especially unfavorable stages [36]. Both daunomycin and adriamycin are highly active in acute myelocytic leukemia (AML) and are additive to combi-

nations that include cytosine arabinoside [64]. There are programs in existence that project an overall gain in 2-year survival to 25–30% [54]. Particularly active are the following induction programs:

1. Daunomycin Cytosine arabinoside	'7 + 3' [64]
2. Daunomycin Cytosine arabinoside Thioguanine	'TAD' [26]
3. Adriamycin Cytosine arabinoside Vincristine Prednisone	'AD-OAP' [54]
4. Daunomycin 5-Azacytidine Cytosine arabinoside Vincristine Prednisone	'D-ZAPO' [2]

As in all programs containing anthracyclines, cardiotoxicity is presently avoided by total dose limitations. A pressing need for circumventing this hazard is evident in an effort to prolong the period of drug administration.

Malignant Lymphomas

The MOPP combination is currently the therapeutic standard in the treatment of advanced Hodgkin's disease [21]. Bleomycin in low dosage is under trial as a nonmyelosuppressive addition to MOPP therapy (BLEO-MOPP). Preliminary reports indicate a higher response rate in direct comparison with MOPP [31]. A satisfactory regimen for patients who have failed MOPP has been developed by Bonnadonna and incorporates adriamycin and bleomycin with vinblastine and imidazole carboxamide [10]. This combination (ABVD) is not crossresistant with MOPP and represents a major therapeutic lead which may improve the rate of cure in this disease.

Likewise, adriamycin has improved the prospects of long term control for the non-Hodgkin's lymphomas, notably the diffuse histiocytic subset. After 6 months of therapy, approximately 40% of patients may enjoy prolonged relapse-free survival and potentially, cure [71]. The most successful current programs involve combinations of adriamycin with prednisone and vincristine (HOP), with the three drugs, plus cytoxan (CHOP, COPA), or the above plus bleomycin (BACOP, CHOP-BLEO) [71, 55, 24].

Childhood Solid Tumors

The most successful applications of antitumor antibiotic therapy have been in Wilms' tumor and embryonal rhabdomyosarcoma [24, 27].

After the original evaluation by Dr. Sidney Farber, the widespread integration of actinomycin D into combined modality therapy has resulted in a cure rate of over 80% in children with localized disease, and up to 60% in patients with pulmonary metastases [20]. Adriamycin and vincristine are likewise highly active and are under investigation in patients with unfavorable presentations [20]. Actinomycin D-containing combinations likewise have been highly successful in an aggressive attack on rhabdomyosarcoma of the embryonal variety in children [27].

Bone Sarcomas

Prior to the application of chemotherapy the prognosis of Ewing's sarcoma was dismal. At least 90% of patients died from metastases. Studies combining actinomycin D, vincristine, and cytoxan (VAC) with aggressive radiation therapy have turned this around with up to 50% disease free survival at 2 years [63]. Currently, adriamycin has been incorporated into this regimen (VAC-ADRIA) in a multidisciplinary intergroup study [58].

Adriamycin is active as palliative therapy in osteosarcoma and may be curative as adjuvant to amputation. It must be given aggressively. Studies by Cortez and Holland have shown that major benefit accrues only to those patients who completed therapy according to doses specified; patients violating the protocol did only modestly better than historical controls [16].

In an effort to reduce the intensity of adriamycin therapy it has been combined with high dose methotrexate [34] or multiple alkylating agents and vincristine [77]. Results of all these programs indicate a 2-year disease-free survival in excess of 50%.

Soft Tissue Sarcomas

Adriamycin is highly active (30%) in this refractory group of tumors [88, 59]. It has been extensively studied in combination with alkylating agents, vincristine and actinomycin D. However, it is not clear that the combinations are definitely superior to adriamycin alone; nevertheless, the duration of response may be prolonged through the use of multiple agents [28].

Kaposi's sarcoma is a special case. The major trials have been carried out at the Uganda Cancer Institute with comparisons of actinomycin D, actinomycin D and vincristine, and actinomycin D and vincristine and imidazole carboxamide (DTIC) [85, 84, 60]. Progressively better results occurred culminating in a 94% complete response rate with the three drugs [60]. The remissions were prolonged but relapse was frequent and the ulti-

mate effect on survival is unknown. Recently this group has reported 60% short term responses with bleomycin used as secondary therapy [83].

Germ Cell Tumors of Testis and Ovary

The chemotherapy of nonseminomatous testicular carcinomas has involved the use of antitumor antibiotics for years, and is best described in tabular form. Drugs of other origin play an important role, as seen in Table 3.

Certainly the combination programs pose problems of enhanced toxicity. The number of actual 'cures' is unknown at present, but it is reasonable to assume it will be higher than the 5% cure rate obtained by actinomycin D, mithramycin, or triple therapy [13].

Germ cell tumors of the ovary have been less extensively studied but triple therapy modifications have been associated with prolonged disease-free survival and probable cure [75].

Trophoblastic Disease

This entity was the first neoplasm to be cured by single agent chemotherapy with methotrexate or actinomycin D [49, 61]. Refinements in technique have led to universal application of the biologic marker, human chorionic gonadotropin [78] associated with this disease, and early treatment for virtually all patients at risk of dissemination [48].

Patients at high risk of death by virtue of markedly elevated (> 100,000 IU) HCG titers, a prolonged course of the disease, or unfavorable metastatic sites (liver, brain, or very extensive lung) are best handled by the immediate use of triple therapy consisting of actinomycin D, methotrexate, and cytoxan [29]. The overall cure rate ranges from 70% for high risk patients to 100% for nonmetastatic trophoblastic disease [48].

Table 3. Chemotherapy of testicular carcinoma

Program	Complete remission %	Reference
Actinomycin D	10+	[13]
Mithramycin	10	[13, 14]
Actinomycin D, chlorambucil, methotrexate ('triple therapy')	12	[50]
Vinblastine and bleomycin	26	[70]
Vinblastine and bleomycin infusion	61	[69]
Vinblastine, bleomycin, cis platinum, actinomycin D (VAB II)	48	[19]
Cytoxan, vinblastine, bleomycin, cis platinum (high dose) and actinomycin D (VAB III)	63	[18]
Vinblastine, bleomycin, cis platinum (Einhorn)	80	[23]

Breast Cancer

Adriamycin is the most active single agent for palliation yet uncovered [7, 88, 59], being non-crossresistant with other agents useful in this common tumor [7, 59]. A short duration of response coupled with potential cardiotoxicity limited its use as a single agent [32]; thus, it quickly moved into various combinations with cytoxan, vincristine, and fluorouracil, principally [37, 22, 65]. Response rates have been impressive in some series, but overall there is no indication that adriamycin adds to duration of response, comparing it to combinations not utilizing this agent [32, 81].

Malignant Islet Cell Tumors

The major therapeutic tool for metastatic or locally inoperable islet cell carcinoma is streptozoticin [72, 11]. This is especially true for insulinomas where the largest experience has accrued. Recently, gastrinomas have been shown to biochemically respond to streptozoticin [17]. The largest collected series, reported by Broder and Carter, indicates 64% biochemical and 50% measurable responses in 52 patients [11]. Survival of responders was doubled compared to nonresponders and historical controls.

Hypercalcemia of Malignant Disease

Mithramycin is clearly the agent of choice in hypercalcemia not associated with bone destruction by tumor and is highly effective in steroid resistant hypercalcemia associated with breast cancer and multiple myeloma [74, 62]. Success with mithramycin is independent of elevated parathormone levels.

Actinomycin D is likewise highly active but has received less investigation [57]. Both agents are active at relatively nontoxic doses, and this effect is independent of antitumor activity.

Other Tumors

The foregoing discussion was limited to those neoplasms where the antitumor antibiotics are firmly established in clinical practice. The following outline will present the

highlights of additional investigations that may result in further clinical indications for therapy with these agents.

1. Malignant Melanoma. Prior use of actinomycin D in 5-day repetitive courses has resulted in moderate response rates alone or with other agents, such as DTIC, vincristine, or nitrosoureas [5]. Recent work on pharmacokinetics has demonstrated a prolonged plasma half-life of actinomycin D [80]. A schedule utilizing large intermittent single doses has resulted and may be active and less toxic [4]. Wide application in melanoma and a number of other tumors will ensue.

2. Squamous Carcinoma: Head, Neck, Cervix, Esophagus. Single agent activity of bleomycin and mitomycin C has been demonstrated and the combination, plus vincristine, has been the most active to date in cervical carcinoma [3].

3. Gastrointestinal Adenocarcinoma. Adriamycin and mitomycin C are active alone in stomach cancer. Since the standard therapy is 5-fluorouracil, it is logical to assume this three-drug combination would be active. Schein et al. have proved it is (50% PR), and long-term results are awaited with interest [53].

4. Lung Cancer. Small cell carcinoma is responsive to a variety of agents and adriamycin has found a major role here combined with other active agents, including nitrosoureas, cytoxan, vincristine, VP 16-213, and procarbazine [73, 1, 14]. When adriamycin, cytoxan, and vincristine are combined with radiation therapy in limited disease, survival is improved [35, 33, 51]. It remains to be seen if it is durable beyond 1 year, as relapse and death have been almost universal beyond that point in other combination programs. Nonsmall cell carcinoma remains an unsolved major therapeutic problem.

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