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Strategies in the treatment of diffuse pontine gliomas: the therapeutic role of hyperfractionated radiotherapy and chemotherapy

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Abstract

This article will review the current treatment of pediatric patients with diffuse pontine gliomas (DPG) and discuss three potential avenues of therapeutic research including (i) radiotherapy (RT) in combination with radiation sensitizers, (ii) dose-intensive, induction chemotherapy with hematopoietic support followed in sequence with RT applied as a 'consolidation' therapy, and (iii) the interleafed application of phase-specific chemotherapeutic agents and hyperfractionated external beam radiotherapy (HFEBRT) referred to as '*chemoradiotherapy*'.

Natural history

The problem

The central problems of neuro-oncology originate with the aggressiveness of central nervous system (CNS) neoplasms, their localization within a critical organ which is relatively inaccessible to pharmacologic agents, and the dose-limiting neurotoxicity of available therapy. The patient with a malignant glioma presents with a tumor volume of 30–60 grams. This represents a mass of $3–6 \times 10^{10}$ cells, of which the neurosurgeon may be able to resect 20–90%. Therefore, a 'best-case' postoperative scenario is a residual tumor burden of 10^9 cells. Megavoltage RT may achieve as much as an additional two-log cytoreduction. Conventionally dosed chemotherapy may contribute a further one-log cell kill. Thus, the patient who completes multimodality therapy may be left with a repository of 10^6 malignant cells that are now presumptively radio- and chemo-resistant [1]. The child afflicted with a DPG poses a greater challenge than other glioma patients as surgical debulking is unrealistic and there is not an alternative method of cytoreduction which is likely to increase the radiotherapeutic response.

Prognostic variables and histopathologic diagnosis

Tumors arising within the brainstem account for approximately 8–10% of the CNS neoplasms of childhood, but are not a single, homogeneous entity. Favorable prognostic features include (a) protracted symptoms, (b) origin within the optic tectum, mesencephalon, or at the cervicomedullary junction, (c) lesions which are cystic, focal and/or dorsally exophytic, (d) onset in adulthood, and (e) neurofibromatosis type I. In contrast, the adverse signs are diffuse pontine infiltration, a high mitotic index, cranioneuropathies and a brief symptomatic prodrome [2–11]. The relative incidence of malignant gliomas (anaplastic astrocytoma, glioblastoma multiforme) observed among children with DPG has been 37 to 100% (mean of 57%) at the time of diagnosis [2–7, 12, 13]. In the Childrens Cancer Group

(CCG) trial # 9882 for brainstem gliomas (BSG), pathologic diagnoses included low-grade astrocytoma (36–38%), anaplastic astrocytoma (46–56%), glioblastoma (6%), ganglioglioma (8%) and non-diagnostic tissue (3–8%) [14, 15].

Indications for surgical intervention

Notwithstanding the histopathologic heterogeneity, the duration of survival among patients with DPG has not been improved by attempted resection [4, 10, 16–19]. Moreover, histologically low-grade lesions behave in a biologically 'malignant' fashion. Hence, the requirement for a pathologic diagnosis of a DPG has become difficult to justify in light of the morbidity, risk of sampling error and the potential for post-operative complications which might delay a more definitive treatment. A *de facto* consensus has emerged within the CCG and Pediatric Oncology Group (POG), that a biopsy is not warranted in cases of DPG with a 'classical' presentation and a diagnostic MRI appearance, as the therapeutic approach employed by current multicenter protocols has not been altered by a specific pathologic diagnosis [15, 19, 20]. Accepted indications for biopsy and/or attempted resection include (a) a focal, enhancing lesion within the midbrain, medulla, cervicomedullary junction or cerebellar peduncle, an exophytic mass within the fourth ventricle, or a cystic mass with a mural nodule, and (b) cases wherein the diagnosis is questionable [6, 15, 19].

Radiotherapy

Historically, 'standard therapy' for the DPG constituted a radiotherapeutic prescription of 45–55 Gray (Gy, 100 rad = 1.0 Gy), delivered in single daily fractions of 180–200 cGy. Most affected children experienced a dose-dependent response with improvement in clinical symptoms. Unfortunately, the median time to progression (TTP) has been only 5 to 7 months with an expected duration of survival of 9 to 13 months [3–5, 12, 16, 21, 22]. In an attempt to improve on these dismal results, HFEBRT has been proposed [23]. Hyperfractionated radiotherapy involves the twice daily administration of smaller fractions, such as 1 Gy separated by 6–8 hours. Pilot and collaborative group studies in the treatment of pediatric patients with BSG have sucessively used doses of 64.8 66, 70.2, 72 and 78 Gy. Response rates, which included patients with stable disease (SD; 0–25% decrease in tumor area), have been reported to be in the range of 62–77% (Table 1). However, these HFEBRT trials have not significantly altered the TTP or provided durable responses [7, 14, 24–27] (Table 1). Hyperfractionated schedules have also not produced a sustained advantage for adult patients with supratentorial malignant gliomas [reviewed by 28].

Justification for further investigation of altered fractionation schedules

Although HFEBRT has been disappointing to date,

Table 1. Results with hyperfractionated radiotherapy among pediatric patients with brainstem gliomas

Dose	Early response rates (%)					TTP	PFS rates (%)			Overall survival (%)			Author
	CR	PR	MR	SD	PD		1 y	20 mo	2 y	1 y	2 y	3 y	
64.8 Gy	7	13	60	13	7	7 mo				48			[24]
66 Gy	0	15		59	21	6.5 mo				48			[25]
72 Gy						44 wks				median survival 64 wks			[7]
72 Gy	6	35		6	3	8 mo		32					[10]
70.2 Gy	2	6		77	15	6 mo				40	23		[26]
66–78 Gy										63	32		[27]
72 Gy	0	16	47	27	11	5.5 mo				38	14	8	[14]

Response rates, time to progression, progression-free and overall survival at 1, 2, 3 years following hyperfractionated radiotherapy of children with brainstem gliomas. Abbreviations include: complete response (CR), partial response (PR), minor response (MR), stable disease (SD), progressive disease (PD), time to progression (TTP), year (y), months (mos), weeks (wks) and Gray (Gy).

it is likely to remain under investigation for the following reasons: (i) The intention of HFEBRT is to exploit the different α/β dose relationships exhibited between non-proliferating normal tissues and malignant tumors. Dose response curves describing the kinetics of cell killing following exposure to ionizing radiation can be characterized using two parameters; one that is proportional to the dose (α), and a second which is proportional to the square of the dose (β) [29]. Repair of radiation damage that occurs during fractionated radiotherapy results in a decrease in the β component. Therefore, a lower α/β ratio implies a greater sparing effect with fractionation. For purposes of comparison, the α/β ratio for the spinal cord is 1.5–2 Gy while that of many tumors is > 10–25 Gy. Thus, increasing the dose fractionation allows for greater repair of the sublethal radiation damage that is sustained by neurons and endothelia within the CNS, in comparison to that of rapidly dividing tumor cells. Theoretically, delivery of the same dose by hyperfractionation affords a comparable control rate while ameliorating the late morbidity of the therapy. Conversely, one can increase the dosage prescription to the tumor from 54 to 72 Gy without risking additional toxicity. (ii) Redistribution of proliferating cells into more vulnerable cell cycle phases may also enhance tumor cytotoxicity without increasing toxicity to the uninvolved brain and its supporting tissues. (iii) Smaller dose fractions may allow hypoxic cells within the core of the neoplasm to reoxygenate [23, 30–32]. Both radiation therapy and chemotherapy are enhanced by good tissue perfusion and oxygenation. Capillary blood flow in white matter is approximately 20% that of gray matter. As the brainstem is extensively myelinated, this may account for the poor results of therapy for BSG. (iv) Expectations regarding potential response and survival rates among BSG patients in preliminary studies and CCG-9882 may have been unrealistic. Radiotherapy by any method offers little more than palliative care to a patient with the extensive, unresectable disease typical of a DPG. The resultant failure therefore may be regarded as a statistically anticipated event, given that RT may effect only a 1–2 log cell kill. The predictability of failure in this setting does not prove lack of efficacy. (v) '... *The radiographic response rate suggests that this therapy might be useful if coupled with other forms of treatment*' [14]. The tumor's response to fractionated RT may be modified by cytotoxic chemotherapy in terms of its repair of sublethal damage, reoxygenation, repopulation and reassortment into different phases of the cell cycle [reviewed by 33]. For example, application of multi-fractionated RT in an alternating administration schema with chemotherapy (e.g., cyclophosphamide) appeared more effective than the additive response seen with single daily fractionation and chemotherapy [34].

Other fractionation schemes, such as hypofractionation, have not received as much attention for DPG. The rationale for hypofractionation is to prevent tumor repopulation during treatment through the use of higher dosages over fewer fractions. The experience to date for the role of hypofractionation in the treatment of adult malignant gliomas has not been encouraging [reviewed by 35]. The recent interest in 'accelerated fractionation' (2 Gy fractions to 60 Gy over 26 days) has been associated with a relative increase in the incidence of the somnolence syndrome and chronic steroid dependence [36]. The literature emphasizes the occurrence of radionecrosis at fractionation schedules greater than 2.5 Gy, total doses exceeding 70 Gy, neurad equivalent therapy (NEURET) doses of 1,450–1,800 cGy and with increasing treatment volume [37–41]. Therefore application of hypofractionation for DPG would probably require 3-dimensional planning or conformal radiotherapy, techniques which themselves are under investigation in some centers.

Chemotherapy

Previous clinical trials

There is little evidence of single-agent chemotherapeutic drugs which are effective against primary or recurrent BSG, as demonstrated by objective neuroradiographic responses (Tables 2 and 3, respectively). Adjuvant nitrosourea-based chemotherapy, i.e. following RT, has not significantly improved survival among children with BSG [45, 72, 73]. In contrast, pre-irradiation chemotherapy ('neo-adju-

Table 2. Chemotherapy of newly diagnosed pediatric patients with brainstem gliomas

Agent(s)	Responses (%)	Duration of response/TTP	Author
HD-MTX	50%	6–12 months	[42]
HD-MTX	80%	7–41+ months	[43]
CCNU, 5-Fu, HU, MISO		Median PFS 32 weeks/median survival 44 weeks	[44]
CCNU, vincristine & prednisone		8 months	[45]
COPP	0%	3–5 months	[46]
'8 in 1'	33% PR		[47]
Carboplatin	1 PR with cervicomedullary glioma	36+ months	[48]
ACNU, interferon-β	91%–27% CR, 64% PR	median survival 15.7 months	[49]
procarbazine, ifosfamide, etoposide, methotrexate, cisplatin & cytosine arabinoside	20% CR, 20% PR, 40% MR, 20% SD	5–23 mo/11–16 mo	[50]
cisplatin, cyclophosphamide	9% PR, 72% SD (to chemotherapy only)	median survival 9 months	[20]
cyclophosphamide, vincristine, cisplatin & etoposide		progression free-survival at 2 yrs 28% 2-yr survival 42%	[51]
carboplatin, vincristine	33% PR, 33% SD		[52]

Responses and their duration among newly-diagnosed children with brainstem gliomas treated with neoadjuvant and adjuvant chemotherapy. Abbreviations include: time to progression (TTP), progression free survival (PFS), high dose methotrexate (HD-MTX), 5-fluorouracil (5-Fu), hydroxyurea (HU), misonidazole (MISO), cyclophosphamide, vincristine, procarbazine and prednisone (COPP).

vant') has demonstrated both feasibility as well as responses [20, 50]. A European regimen combined procarbazine (cycle I: 100 mg/m^2 for 10 days), continuing with cycle II comprised of ifosfamide (3 gm/m^2 for days 1–3), etoposide (150 mg/m^2 on days 4–6), then followed 8 days later by cycle III utilizing methotrexate (5 gm/m^2 weekly × 2), until cycle IV with cisplatin (40 mg/m^2 on days 1–3) and cytosine arabinoside (400 mg/m^2 on days 1–3) during the third consecutive week. Cycles II–IV were repeated after a 3 week interval and patients were then treated with HFEBRT (63.8 Gy). Responses are shown in Table 2. Three of five children were alive and without evidence of tumor progression for a mean of 11.8 months (range 4–23 months). The two deaths at 11 and 16 months were due to progressive disease (PD) [50].

The POG-8833 study of pre-irradiation chemotherapy and HFEBRT for BSG treated 32 evaluable, newly-diagnosed patients with four induction cycles of cisplatin (100 mg/m^2/course) and cyclophosphamide (3,000 mg/m^2/course) followed by HFEBRT (66 Gy). While clinical responses were reported in 65%, objective neuroradiologic review delineated partial responses (PR; > 50% cytoreduction) in 9.4%, SD in 71.9% and PD in 18.8% following induction chemotherapy (Table 2). There were no complete responses (CR). The pharmacologic toxicity was both hematopoietic and neurologic. Only 50% of patients completed the four scheduled cycles of induction, which may be attributable to the fact that this protocol was administered without granulocyte colony stimulating factor (G-CSF). There were two toxic deaths following the fourth induction course of chemotherapy. The neurologic status of two patients deteriorated transiently, apparently because of hyperhydration. Following HFEBRT, 20% exhibited a PR, 60% SD, while 20% suffered PD. Six children developed transient myelosuppression following HFEBRT. While the 3/32 children who experienced a PR during induction demonstrated the longest survival intervals (≥ 38–44 months), the majority of children died because of PD. The 1-year survival was 30%; the 1-year progression-free survival (PFS) was 16%. There was no correlation between responses to chemotherapy and HFEBRT. The median survival of 9 months was not significantly different from the previous POG experience with HFEBRT at 66 Gy [20, 25].

Table 3. Chemotherapy of pediatric patients with recurrent brainstem gliomas

Agent(s)	Responses (%)	Duration of response	Author
Cyclophosphamide	80% PR	3–11 months	[53]
Cyclophosphamide & vincristine	1 PR/SD	39+ months	[54]
COPP	33% SD (1 pt with cervicomedullary glioma)		[46]
Carboplatin	0%		[55]
Carboplatin	13% PR, 13% SD	4–5 months	[56]
Carboplatin	5% PR, 21% SD	9–46+ months	[57]
Carboplatin	3% PR		[58]
Cisplatin	17% PR		[59]
Cisplatin	0%		[60]
Cisplatin	0%		[61]
Cisplatin	29% with SD	1–4 months	[62]
Iproplatin	0%		[58]
Diaziquone	8% SD		[63]
PCNU	18% PR, 9% SD		[64]
PCNU	18% PR, 12% SD		[65]
'8 in 1'	0%		[47]
MOPP	19% PR, 13% SD	5 months	[66]
5FU, CCNU, HU & 6MP	69% SD	25 weeks	[67]
Ifosfamide & etoposide	13% PR, 13% SD	7+ months	[68]
Cisplatin, etoposide & Cytosine arabinoside	0%		[69]
Thiotepa	29% SD	3–5 months	[70]
VP-16/Etoposide	8% CR, 25% PR, 17% SD	4–20 months	[71]
Carboplatin, vincristine	50% PR (1/2)		[52]

Responses and their duration among children with recurrent brainstem gliomas treated with neoadjuvant and adjuvant chemotherapy. Abbreviations include: time to progression (TTP), 5-fluorouracil (5-Fu), hydroxyurea (HU), 6-mercaptopurine (6MP), cyclophosphamide, vincristine, procarbazine and prednisone (COPP).

Current clinical trials of the Childrens Cancer Group

The CCG-9882 observed PD at 5.5 months following diagnosis despite the incorporation of HFEBRT. This generated the hypothesis that dose-intensive chemotherapy, with hematopoietic support, might induce a cytoreductive response which could then be 'consolidated' with HFEBRT prior to the predicted TTP at the 5^{th}–7^{th} month. Derived from the experience reviewed above, the CCG-9941 Phase II trial for BSG has recently opened and randomizes patients between two arms for three cycles of induction chemotherapy with G-CSF support. Regimen A includes carboplatin (1,200 mg/m^2/cycle), etoposide (498 mg/m^2/cycle) and vincristine (4.5 mg/m^2/cycle) while regimen B is comprised of cisplatin (100 mg/m^2/cycle), cyclophosphamide (3,000 mg/m^2/cycle), etoposide (300 mg/m^2/cycle) and vincristine (4.5 mg/m^2/cycle). Responses are assessed after induction. The patients will then advance to HFEBRT (72 Gy) after which they will be reevaluated. This protocol is proposed to add future arms as data from current pilot studies mature. For example, there has been recent, encouraging experience with the protein kinase C inhibitor, tamoxifen, as a single agent in the treatment of recurrent BSG [A. Freeman and M. Hetherington, personal communication]. This interest is based upon *in vitro* and clinical investigation which has demonstrated efficacy at micromolar concentrations against recurrent malignant gliomas [74, 75]. A preliminary trial is investigating the combination of carboplatin (800 mg/m^2/cycle) and etoposide (500 mg/m^2/cycle) with a dosage escalation trial of tamoxifen for recurrent/progressive malignant gliomas [I.F. Pollack, personal communication].

Future considerations

Analysis of the literature would suggest that, with extant agents, technology intensification of the pharmacologic prescription offers the most feasible intervention to improve response rates and survival. Radically innovative surgical and radiotherapeutic techniques will probably remain of limited applicability for the DPG in the foreseeable future.

Radiosensitizers

The divided daily schedule of HFEBRT lends itself to coadministration with radio-enhancing agents in an outpatient setting. These may be thought of as being in one of three types: (a) classical radiosensitizers such as halogenated pyrimidines, (b) hypoxic cell sensitizers such as the nitroimidazoles and (c) conventional chemotherapeutic drugs which enhance radiotoxicity in a multifactorial fashion. Bromodeoxyuridine and iododeoxyuridine increase radiochemical injury, largely through inhibition of the repair of radiation-induced DNA damage. These agents have been studied with both conventional and hyperfractionated administration schedules but have not received widespread acceptance [reviewed by 35, 76, 77]. Previous trials with hypoxic cell radiosensitizers, such as the nitroimidazoles – misonidazole or metronidazole, have not yielded the predicted clinical benefit in the treatment of malignant gliomas [reviewed by 35, 76, 78–80]. Agents designed to overcome tumor core hypoxia, such as the perfluorochemical emulsion Fluosol, remain largely of academic interest in the treatment of CNS malignancies [81, 82]. The radiosensitizing chemotherapy drug, hydroxurea, has been used in combination with RT with marginal, if any, improvement in survival [35]. Trials of cisplatin with RT for solid tumors are reviewed below.

Newer possibilities include nicotinamide, inhaled carbogen, taxol, the topoisomerase inhibitors such as topotecan, and certain 'older' chemotherapeutic drugs which are under study for new indications [83]. The G_2 and M phases are the most radiosensitive portions of the cell cycle, therefore chemotherapeutic agents which are specific for these phases may enhance radiation's cytoreductive potential. Taxol is a potent microtubule stabilizing agent which selectively arrests cell cycle progression during the G_2/M phase to effect cytotoxicity in a time-concentration dependent manner. Experimental work with a radioresistant malignant glioma cell line, G18, has suggested that taxol may also be a potent radiosensitizing agent. Cell killing was concentration-dependent with a sensitizer-enhancement ratio for 10 nM taxol at 10% survival being approximately 1.8. Incorporation of taxol into an appropriate protocol may provide a relative advantage over RT alone [84].

The topoisomerase inhibitors interfere with DNA synthesis through strand breakage, which correlates closely with cytotoxicity. The topoisomerase I inhibitor, topotecan, also has a radioenhancing effect. The mechanism appears to be mediated by the generation of irreversible DNA-topoisomerase I complexes which prevent repair of DNA injury, thus creating lethal double-strand breaks. In an *in vitro* melanoma model system, radiation dose-enhancement ratios of 2.0 or more were obtained with topotecan doses that were significantly less than required for cytotoxicity with the drug itself [85–87].

Dosage intensification of the chemotherapeutic prescription

The Norton-Simon hypothesis predicts that a tumor's rate of regression is a direct function of chemotherapeutic and radiotherapeutic dosage, as well as the growth rate of the tumor prior to the initiation of treatment [88]. Experience has shown that dose-intensive, multidrug protocols will be necessary to induce responses among newly-diagnosed DPG patients. The challenge of this approach is to combine potentially synergistic agents acting within different phases of the cell cycle but without overlapping toxicities.

Availability of synergistic drug combinations

Platinum and etoposide are thought to have more than an additive interaction in a number of tumor types. A recent trial of this combination (cisplatin 45 mg/m^2 and etoposide 360 mg/m^2/course) in newly-

diagnosed adult patients with malignant gliomas showed a 55% response rate and 26% SD rate among glioblastoma patients, when treated before and after RT. The TTP was delayed as long as 38.5 weeks among the glioblastoma patients and to 73 weeks among anaplastic astrocytoma patients [89]. Among newly-diagnosed medulloblastoma and primitive neuroectodermal tumor patients, cisplatin (90 mg/m^2/course) and etoposide (300 mg/m^2/course) demonstrated a 18% CR and 73% PR rates, achieving PFS intervals of 3–48+ months [90]. Cisplatin has been used in concert with etoposide and cytosine arabinoside for recurrent childhood malignant gliomas with 19% CR and 13% PR rates [69]. Cisplatin (20 mg/m^2/d for 5 days) and etoposide (75 mg/m^2/d $\times$ 5 days) have been combined for the deferral or postponement of RT among infants with malignant CNS tumors. Among malignant gliomas, primitive neuroectodermal tumors and ependymomas, the CR rate was 38%, the PR rate was 13% with the median TTP being 17.5 months and the median survival 34 months [91]. High dose carboplatin (1,000 mg/m^2/course) has been used in conjunction with etoposide (300 mg/m^2/course) for newly-diagnosed and recurrent CNS neoplasms. The overall response rate was 100% for pretreated and 88% in previously untreated patients. There were 3/4 CR among recurrent medulloblastoma, 2/2 PR for untreated and 2/2 minor responses (MR) for recurrent malignant glioma patients [92]. Etoposide has also been combined with ifosfamide with demonstrated efficacy (Table 3) [68].

The 'baby POG' regimen was devised for the treatment of CNS malignancies in infants, for whom RT was considered unacceptably toxic [51]. The protocol design consisted of alternating 28 day cycles of AAB-AAB, in which Regimen A consisted of cyclophosphamide (65 mg/kg or 1,950 mg/m^2/course) and vincristine (0.13 mg/kg/course) and Regimen B was cisplatin (4 mg/kg, 120 mg/m^2/course) and etoposide (13 mg/kg, 390 mg/m^2/course). This combination has yielded 'very encouraging' results among infants with malignant gliomas and BSG. The 2-year PFS and overall survival rates were 54% and 65%, respectively, in children with malignant gliomas, which exceeded those achieved in older children treated with postoperative RT alone (PFS 20%, overall survival 40%), RT with CCNU-vincristine-prednisone or the 'eight in one' combination chemotherapy with RT [51, 93, 94]. Similarly, the 28% 2-year PFS and 42% 2-year survival rates among patients with BSG were superior to results obtained with HFEBRT in children less than 6.7 years (Table 2) [27, 51].

Dosage intensification of synergistic drug combinations

High dose regimens of cyclophosphamide (5,000 mg/m^2/cycle), etoposide (1,500 mg/m^2/cycle), cisplatin (150 mg/m^2/cycle) have been combined among adult patients *without* the support of peripheral blood stem cell (PBSC) harvesting or autologous bone marrow transplantation. Twenty-five percent of evaluable patients with advanced systemic malignancies experienced a CR and 36% achieved a PR. The important observation was that the degree of response correlated with delays in TTP. While the hematologic toxicity was not dose-dependent, the dose-limiting toxicities proved to be pulmonary and cardiac. Only 8 of 42 patients tolerated 3 or more cycles [95]. A similar induction regimen using cyclophosphamide (4,500–5,250 mg/m^2/cycle), etoposide (750–1,200 mg/m^2/cycle), cisplatin (120–165 mg/m^2/cycle) was subjected to randomized comparison with or without autologous bone marrow transfusion. This study of 92 patients demonstrated an advantage in time to hematologic recovery for the transplantation arm [96]. A more recent trial has extended this experience utilizing two cycles of high dose cyclophosphamide (4,500 mg/m^2/cycle), etoposide (900 mg/m^2/cycle) and cisplatin (150 mg/m^2/cycle) with the support of G-CSF and PBSC among lung cancer and head-neck cancer patients. Of 11 evaluable patients, 36% experienced a CR for 2–20 months; the majority were newly-diagnosed. Thirty six percent of patients experienced a PR, most of whom had been heavily pre-treated. There were 3 deaths (27%) soon after the first cycle. Stimulation of PBSC with G-CSF or granulocyte-macrophage colony stimulating factor (GM-CSF) shortened the period of hematologic recovery significantly [97].

Dose intensification with the support of peripheral blood stem cells

A number of investigators have hypothesized and

demonstrated dose-intensity dependent responses which are achievable only if the inherent dose-limiting toxicity of myelosuppression can be overcome. Of note, the relatively low growth fractions of solid tumors limit the effectiveness of phase-specific agents administered with only brief exposure times. The autologous bone marrow transplant regimens have intensified the peak dose by administering ultra-high doses over a short period. Such trials have had little to show in the way of efficacy among adult malignant gliomas [98, 99]. The feasibility of repetitive chemotherapy protocols which emphasize the peak dose and time-intensity concepts has become possible with the development of PBSC support [98]. The major advantages of PBSC harvesting are (a) it allows successive cycles of chemotherapy to exploit 'area under the curve' effects [100]. (b) It obviates the anesthetic risks of repeated bone marrow harvesting [101]. (c) Autologous PBSC engraft faster than autologous bone marrow after high-dose chemotherapy and/or RT because they are enriched with circulating mononuclear cells and contain primitive pluripotential stem cells which replenish committed progenitor cell pools to provide sustained long-term engraftment [reviewed by 101, 102].

High-dose cyclophosphamide, carboplatin, taxol, etoposide and/or ifosfamide have been successfully used for mobilization of PBSC. Use of chemotherapeutic agents, such as cyclophosphamide and etoposide which spare the stem cell compartment, appear ideal for mobilization of PBSC's [103]. This effect is potentiated when these drugs are administered prior to growth factors such as G-CSF or GM-CSF [reviewed by 102, 103]. This supportive technique has had significant impact on the treatment of the hematologic malignancies, allowing dramatic escalation in dose-intensity with corresponding improvement in response rates [reviewed by 103]. The role of PBSC in the treatment of solid tumors remains under investigation, although it may be more helpful in the management of tumors which display steep dose-response curves [reviewed by 98, 103]. The high dose chemotherapy afforded by PBSC harvesting has increased the 2-year PFS rates among patients with metastatic breast cancer to 20%, and to > 70% for patients with high risk local disease [reviewed by 100]. To date, there has been little experience with PBSC harvesting in the treatment of brain tumor patients [104].

'Chemoradiotherapy'

Chemotherapy and RT may be closely interleafed for dosage-intensification in a manner that further potentiates the cytoreductive response beyond that of radiosensitization in order to overcome local disease resistance [105]. The theoretical justifications for combining phase-specific chemotherapeutic agents and HFEBRT simultaneously, sequentially, or in an alternating fashion include: (a) Repetitive chemotherapy may circumvent the intrinsic resistance of solid tumors caused by relatively large numbers of cells remaining in G_0 phase. An initial course might induce resting cells to cycle into the radiosensitive G_2-M phases, rendering them susceptible to RT in later treatment cycles. Conversely, radiation-induced cytoreduction may increase 'reactive proliferation' within the neoplasm and perhaps provide cell cycle synchronization which may serve to enhance sensitivity to phase-specific chemotherapeutic agents. (b) Certain chemotherapeutic drugs may contribute to the inhibition of repair of sublethal radiation damage or recovery from a potentially lethal radiotherapeutic injury (*vide infra*). (c) Decreased tumor cell repopulation following fractionated RT may be due to the effects of chemotherapy. (d) Early cytoreduction may prevent the emergence of chemo- and/or radio-resistance subpopulations upon tumor regrowth, as *a priori* cross-resistance is presumed to not exist between neoadjuvant chemotherapy and RT. (e) Combination therapy may address cell cycle phase heterogeneity and differential tumor cell sensitivity, due to local conditions such as hypoxia and acidosis. For example, tumor core re-oxygenation may occur following chemotherapy treatment thus improving the radioresponsiveness of the neoplasm. Conversely, improved drug delivery may result from better perfusion due to cytoreduction or a radiation-induced disruption of endothelial function and blood-brain barrier integrity [modified from 98, 106–109].

The interaction of radiotherapy and phase-specific chemotherapeutic agents

Chemotherapeutic agents produce two types of cytoreductive effects: (a) a log linear dose-response relationship or (b) a initial log linear dose effect followed by a plateau phase, which is not dose-responsive. The first pattern is typified by alkylating agents which bind DNA, for which dosage escalation progressively causes a greater fractional cell kill. The second is found with certain phase-specific agents such as the vinca alkyloids and epipodophyllotoxins. These latter agents demonstrate significant time dependency with respect to their quantitative cell killing. Prolongation of drug exposure tends to eliminate the plateau phase as more cells pass through the vulnerable phase of the cell cycle. However, the response may be lost on protracted or repeated exposure as the tumor cell population enlarges and resistance emerges [reviewed by 107]. Of currently available agents, the alkylators are least prone to the development of resistance. At least two alkylators, cyclophosphamide and cisplatin, are likely to be independently effective in enhancing the cytoreductive effect of RT in this type of strategy.

Cyclophosphamide functions as an alkylator of DNA; it also decreases DNA synthesis. The drug's greatest effect is inflicted in late G_1, early S and M phases. Cyclophosphamide interacts with RT to decrease repair of sublethal radiation damage and so increase radiosensitivity [110]. Experimental studies have shown an additive effect on tumor growth delay when RT is administered 11, 7, 4 or 1 days prior to cyclophosphamide. In contrast, the sequence of cyclophosphamide followed 4, 7 or 11 days later by RT produced significantly greater delays in regrowth ($p \leq 0.005$). Coadministration in this experimental model demonstrated no advantage over sequential treatment. However, alternating cyclophosphamide and RT at intervals of 7 days allowed asynchronous hematopoietic and mucosal recovery over the 14 day period between respective treatments. As noted earlier, multifractionated RT was superior to alternation with daily fractionation in this model [34, 109].

Cisplatin acts through the formation of inter- and intra-strand cross-linking of DNA. Cells deficient in DNA repair capacity are particularly sensitive to its bifunctional alkylating effect. This agent is generally not considered a phase-specific agent but it does appear to be more active in G_1 [110]. Cisplatin's interaction with RT causes two types of cytotoxic damage: inhibition of the repair of sublethal radiation damage and chemical interaction with DNA mediated by free radicals. It may also serve to increase the slope of radiation dose-response curves for hypoxic cells [105, 110, 111].

'Preradiation enhancement' may occur as a direct result of such cisplatin effects on both hypoxic and oxygenated cells at the time of administration of RT. 'Postradiation enhancement' may be mediated by inhibition of the repair of sublethal radiation damage [106]. *In vivo* experimental protocols suggest a supra-additive response occurs at a dosage schedule of 2.4 mg/kg/d (72 mg/m^2/d) $\times$ 5 days given immediately prior to RT (1,000 r/day $\times$ 5 days). This scheme also produced less aggravation of normal tissue toxicity in C3H/Km mice [112]. However, the enhancement achieved by 12 mg/kg (360 mg/m^2) cisplatin given 24 hours prior to the start of fractionated daily RT may be comparable [113].

A variety of schedules for cisplatin with RT have been piloted among patients with head-neck or lung cancer, where its role as a radiation enhancer continues to be investigated [105, 106, 110, 114–116]. A recent trend has been to combine cisplatin (6 mg/m^2/day $\times$ 5 days/week for 6 weeks) with multiply fractionated RT, as the EORTC and SWOG has found this superior to either weekly administration (30 mg/m^2) or single-fraction RT in terms of TTP and overall survival in lung cancer. The toxicity has been acceptable [reviewed by 117]. The effectiveness of this lower dosage has encouraged coadministration with etoposide (20 mg/m^2/day $\times$ 5 days/week) during weeks 1–2 and 5–6 of RT [106]. The efficacy of cisplatin-based combined treatment in the control of non-small cell lung cancer has been supported statistically in 4/10 studies with 3/10 being of borderline significance [reviewed by 117]. However, the EORTC Brain Tumor Group has not found cisplatin (60 mg/m^2) administered on days 1, 8, 15 and 21 of radiation to significantly impact TTP or survival among adult malignant glioma patients [118]. The current POG-9239 protocol for BSG is

studying the role of platinum chemotherapy as a radioenhancing agent. The randomized design used is to administer cisplatin (100 mg/m^2/course) over a 120 hr continuous infusion schedule on weeks 1, 3 and 5 during conventional radiotherapy (54 Gy) or HFEBRT (70.2 Gy). This dosage regimen was previously piloted through POG-9139 and a St. Judes' Childrens Research Hospital institutional trial from 25 to 100 mg/m^2/week [L. Kun, personal communication].

There are other phase-specific agents which may be of value in chemoradiotherapy. The topoisomerase II inhibitor, etoposide, has been more widely tested than topotecan (reviewed above); however, there is limited *in vitro* or clinical data to suggest a radiosensitizing role for this agent [reviewed by 119]. Nonetheless, etoposide is increasingly being coadministered with cisplatin, cyclophosphamide, adriamycin and/or vincristine in conjunction with RT for lung cancer. Radioenhancement seems possible as stable ternary complexes are formed by etoposide with DNA and topoisomerase-II. The enzyme then attaches covalently to DNA forming single-strand protein-associated breaks. Etoposide may also exert a cytotoxic effect through metabolic activation of reduction-oxidation reactions, the derivatives of which bind DNA. The vinca alkyloids function by binding tubulin, thus inhibiting microtubular assembly with disruption of the mitotic spindle apparatus and arrest of cells in metaphase. This produces an accumulation of cells in M phase, suggesting that vincristine should have a radiosensitizing effect. However, most experimental work has been conducted with vinblastine, vindesine and a synthetic microtubule inhibitor, tubulozole-*cis* [reviewed by 119].

Choices in the schedules of administration

Simultaneous: The Goldie-Coldman model predicts that simultaneous administration would minimize the emergence of resistance to chemotherapy and RT. However, their combined toxicity may allow only intermittent coadministration. *'Most experimental and clinical data suggest that enhanced tumor effects most often result from simple additivity and therefore do not require direct interaction between drug and radiation, whereas enhanced normal tissue effects are observed most often when drugs are administered in close temporal proximity to radiation. Thus, for optimal therapeutic effect, it would seem advantageous to administer chemotherapeutic drugs and radiation in a sequential or alternating manner rather than simultaneously'* [111].

Sequential: The advantage of sequential treatment is to render toxicity more tolerable, however the reduction in intensity may allow tumor repopulation and the emergence of resistance. Sequential administration of cyclophosphamide in an experimental model demonstrated progressive deterioration in the cytoreductive response: cytoreduction was followed by maximal rates of regrowth every 13–15 days such that there was acceleration of regrowth until resistance appeared to emerge following the 4th course [109]. The clinical experience with neoadjuvant chemotherapy of head-neck and anal canal cancers has borne this out as improvement in local disease control has failed to translate into improved survival [reviewed by 108]. Similarly, the POG-8833 trial observed an initial improvement in most children with BSG treated with induction chemotherapy which was later followed by progression, suggesting that tumor resistance emerged after 3rd–4th cycle [20].

Alternating: Rapid alternation of chemotherapy and RT may provide temporal dispersion of therapy, avoid compromise of dosage-intensity but allow for affordable toxicity. An important consideration is whether the intent is maximal control of local disease or metastatic disease burden (*'spatial cooperation'*). In clinical practice where distant disease failure is common, this modeling approach would suggest the early application of RT rather than reserving it for 'consolidation' [reviewed by 107]. The clinical problem among DPG is local disease control, thus favoring the neoadjuvant application of the chemotherapy. The theoretical advantages are (i) to minimize the acquisition of resistance to either modality and (ii) elimination micrometastases or infiltrating tumor cells in the vascularized margin with early chemotherapy. The

potential disadvantage is the split in the radiotherapeutic prescription. An alternating schedule of chemotherapy and multifractionated RT provided more effective disease control than either alternating single fractionation schemes with chemotherapy or sequential administration in the Looney-Hopkins model. The validity of this approach has been supported by its clinical application in the treatment of small cell lung cancer and head-neck cancers [reviewed by 107, 109, see also 120, 121].

A proposed model of chemoradiotherapy for diffuse pontine gliomas

Within 3–14 days of neuroradiologic diagnosis and PBSC harvesting, the patient will begin induction chemotherapy with dose-intensive cyclophosphamide (CPM), etoposide (VP16), vincristine (VCR) and cisplatin (cDDP). These will be administered as in an in-patient setting over a 5 day period, every 21–28 days for 2 cycles. G-CSF stimulation will be used for mobilization of PBSC for the initial harvesting. Marrow reconstitution with PBSC and G-CSF will also be used to shorten the period of pancytopenia. Reinfusion of PBSC will occur 24 hours after the final dose of chemotherapy.

Patients will be reharvested when the recovering WBC reaches ≥ 1,000, which is anticipated to be day 17 (± 2 days). Two cycles of chemotherapy are planned prior to the initiation of alternating chemotherapy in order to simplify the radiotherapeutic prescription.

Roadmap for Induction Phase cycles # 1 and 2

Week	1					2		3			4
Day	1	2	3	4	5	6	8	15	16	17	21 or 28/0
CPM		XXX									(3,000 mg/ m^2/cycle)
VP16	XXXXX										(500 mg/ m^2/cycle)
c-DDP			X								(100 mg/ m^2/cycle)
VCR	X						X	X			(4.5 mg/m^2/ cycle)
G-CSF						→→→→→→→→→→→→→→→→→→					
PBSC reinfusion						X					
PBSC harvest										XX	

Cycles # 3 and 4 of chemotherapy will be alternated with HFEBRT which is to be administered over 9 days. Reinfusion of PBSC will again occur 24 hours following the final dose of cisplatin. HFEBRT will also begin within 24 hours of the last cisplatin dose. Patients will be reharvested when the recovering WBC reaches ≥ 1,000, which is anticipated to be day 17 (± 2 days).

Induction Phase cycles # 3 and 4 of Chemotherapy alternating with 2 courses of HFEBRT

Week	1					2		3			4
Day	1	2	3	4	5	6	8	12	15	16 17 19	21 or 28/0
CPM		XXX									(3,000 mg/ m^2/cycle)
VP16	XXXXX										(500 mg/ m^2/cycle)
c-DDP			X								(100 mg/ m^2/cycle)
VCR			X					X		X	(4.5 mg/ m^2/cycle)
G-CSF			→→→→→→→→→→→→→→→→→→								
PBSC reinfusion			X								
PBSC harvest									XX		
HFEBRT			XX	XX	XX	XXX					(100 cGy bid × 9 d = 18 Gy)

During induction, HFEBRT will be administered only to the involved field of the postoperative residual disease and its margin. The dosage prescription will consist of 18 Gy to the involved field, administered as 100 cGy fractions twice daily for each of two periods of 9 days to complete 36 Gy. Following the completion of the fourth cycle of induction chemoradiotherapy, patients will then complete the full radiation prescription of 72 Gy, given as an uninterrupted course of 36 Gy in twice daily fractions of 100 cGy.

Timing of the administration of the radiosensitizer, cisplatin.

Large and infrequent, rather than small and frequent, individual administrations of cisplatin are better used with radiation for enhanced therapeutic effectiveness. Administration of cisplatin close in time to radiation is best for therapeutic response, although perceived efficacy follows from rather flexible integrations of these two modalities' [105, see also 106]. It is unlikely that the tissue concentrations of cisplatin achieved with daily administration are sufficient for effective radiation chemical-based potentiation. Administration of cisplatin prior to RT is based upon the assumption that much of the ther-

apeutic gain is due to cisplatin-mediated inhibition of repair of sublethal radiation damage [105]. The interval between preadministration of cisplatin and RT varies with the model chosen from shortly before to as long as 24 hours prior [reviewed by 114]. In comparing the enhancement ratios achieved by the interaction of cisplatin and a course of 5 daily RT treatments on SCCVII/St tumor and normal tissues within the C3H mouse, combination treatment with cisplatin 24 hours prior to the radiotherapeutic prescription appeared to produce high therapeutic gain against the neoplasm while minimizing the enhancement ratios for normal tissues [122]. These theoretical concerns must be taken within the context of a dosage-intensive protocol for DPG which is likely to utilize PBSC. Due to the practical concerns of allowing engraftment of the PBSC, which would be administered during the alternating chemo-radiotherapy, concurrent low-dose cisplatin and HFEBRT may not be desirable. It appears preferable to administer standard dose cisplatin (100 mg/m^2/cycle) on the final day of chemotherapy infusion. This would be followed 24 hours later by the initiation of HFEBRT for that cycle and reinfusion of the PBSC.

We hypothesize that this strategy could deliver 2 cycles of chemotherapy alone followed by 2 cycles of alternating chemotherapy and HFEBRT within 12–16 weeks (2.8–3.7 months; 84–112 days) with the support of PBSC reinfusions and G–CSF. This is well within the anticipated time of progression of residual disease at 5.5 months (23.7 weeks, 166 days) and would be superior to our preliminary experience, which completed induction at 17.2 weeks (4 months; 120 days) (unpublished data). This would allow evaluation of the role of dose-intensive chemoradiotherapy in the achieving responses and delaying TTP among children with DPG.

In conclusion, the PDG has proven to be a neoplasm refractory to conventional therapy. The thesis of our recommended approach has been to escalate therapeutic intensity in a manner predicted by the Norton-Simon and Looney-Hopkins models to be potentially effective. While this one protocol is hardly definitive, the failure of this methodology should occasion a serious reevaluation of our therapeutic approach. One specific suggestion would be to consider patients with newly diagnosed DPG as eligible for Phase I trials of preradiation chemotherapy. The current practice of restricting Phase I agents to patients who have exhausted conventional and Phase II chemotherapeutic agents and RT has two undesirable and heretofore unavoidable results. These patients are less able to tolerate dosage escalation to approximate the maximum tolerated dose for a naive individual. The previous treatment increases the likelihood that acquired resistance will mask the therapeutic efficacy of the Phase I agent. Preliminary results of toxicity (and efficacy) with attractive agents, such as temozolamide, could be ethically expanded among a cadre of patients whose disease has been shown to defeat available means of intervention.

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