3. Treatment

3.1. Neurosurgery (by Armando Cama, Genova)

Surgical decompression by laminectomy has been for long time the almost unique treatment modality for epidural compression detected at diagnosis in children with neuroblastoma [6]. Neurosurgeons have always recognised this entity as a true surgical emergency in reason of the peculiar anatomic and vascular features of the spinal cord making it extremely sensitive to any type of injury. Severity of spinal cord damage correlates with site of compression (being more severe at cervical and upper dorsal levels), tumour extension in the spinal canal, and duration of compression. In absence of effective therapy, neurological function tends to deteriorate leading to permanent deficits. In the late 80s, along with the remarkable improvement in diagnostic imaging and the refinement of supportive measures, chemotherapy started to be considered as an alternative therapeutic approach, its main advantage being a lower risk of orthopaedic sequelae. Consequently, the issue of how to treat a child affected by neuroblastoma presenting epidural compression has become matter of strong debate, eventually making it compelling to reach a consensus. At the present, surgical decompression should possibly be considered the preferable option in case of rapidly neurological worsening and of lack of improvement during the administration of chemotherapy. Neurosurgery may also be indicated when the diagnosis of neuroblastoma needs confirmation, as it may occur when catecholamine excretion is normal and bone marrow is free of tumour infiltration.

3.2. Radiation therapy (by Giulio J D'Angio, Philadelphia)

Radiation therapy can be delivered easily and promptly to a small paravertebral tumour with intraspinal extension through the use of a single, posterior field [7]. Larger tumours may require anterior as well as posterior fields to obtain dose homogeneity. A straightforward technique is to deliver 300 cGy to the mass on each of 3 successive days since there is always some urgency, else radiation therapy would not have been elected. The effect on normal growth and development after such a dose given to a field 3–5 vertebral bodies in length is negligible even in babies. Perhaps 3 cm of shortening in total height at maturity can be expected after such irradiation given to an infant. Late effects on the thyroid are the major concern when the neck or upper thoracic spine is treated. This is because even very low scattered doses of radiation can cause trouble with function, and/or give rise to growths, both benign and malignant. More modern techniques are available that localize the radiation therapy very precisely to the tumour volume. Adjoining tissues and structures receive only a fraction of the tumour dose, but these methods require more elaborate planning that may take days. The treatment time is also longer; that is, the time the child must lie still on the table. This is essential if the full advantages of these methods are to be enjoyed. Anaesthesia may then be necessary in children who cannot cooperate because of young age or temperament. The problems with post-irradiation thyroid difficulties after upper spine radiation therapy also are not obviated, because the gland receives scattered radiation even under the most stringent limitations of field edges. On balance, the simpler field arrangements are probably the best given the setting in which radiation therapy is to be employed. They are quick, and easy to do.

3.3. Chemotherapy (by Bruno De Bernardi, Genova)

The effectiveness of first line chemotherapy in dumbbell neuroblastoma was first reported by Hayes et al. [8] in 1984. Nine of 11 children with neurological symptoms recovered completely and two remained paraplegic. In 1989, Sanderson et al. [9] reported two children with paraplegia and two with paraparesis, who fully recovered being treated with OPEC Regimen. Based on these favourable results more and more children with epidural neuroblastoma have subsequently been spared a neurosurgical intervention. However, the identification of which children can be safely treated by chemotherapy alone has not been clarified yet although in this mini-review two series report on children treated prevalently or exclusively by chemotherapy.

4. Clinical experiences

4.1. Italy (Maria Luisa Garré, Genova)

The Italian Cooperative Group for Neuroblastoma published in 2001 a series of 76 cases of symptomatic epidural compression that occurred in 1462 children with neuroblastoma recruited between 1979 and 1998 [10]. Chemotherapy and decompressive laminectomy had comparable ability to relieve neurological symptoms, although none of the children presenting with paraplegia recovered.

Based on this retrospective study, children with neuroblastoma presenting with symptomatic epidural compression in the subsequent period 1999–2003 were preferentially treated with chemotherapy and followed prospectively. They are the object of the present report.

4.1.1. Patients and methods

Children with previously untreated neuroblastoma and symptomatic epidural compression at diagnosis were included in this analysis. Data concerning symptoms and neurological status at presentation, time elapsed between first symptoms and diagnosis, initial therapeutic approach, and neurological outcome were registered. Motor impairment was scored as follows: *grade 1*, mild hypostenia with walking disability for legs, poor difficulty in raising hands above head for arms; *grade 2*, moderate hypostenia with inability to walk and make movements against gravity, or raise hands above head; *grade 3*, severe hypostenia with paraplegia, no elicitable tendon reflexes or muscular movements.

4.1.2. Results

Of a total of 530 children with neuroblastoma 26 (4.9%) presented with symptomatic epidural compression. Eleven were male and 15 female. Age ranged form 0 to 18 years (median, 14 months). Follow-up ranged from 12 to 55 months (median, 22). Patient demographics, neurological presentation and treatment are shown in Table 1 and look comparable to the previously published series, but for the severity of motor impairment at diagnosis.

Five patients presented with motor deficit of grade 1, 16 of grade 2 and five of grade 3. Ten children complained of back pain, 10 had sphincteric and five had sensitivity dysfunction. Eight out of 26 children epidural compression was treated by laminotomy. Three of them did not receive additional treatment, and five received chemotherapy according to disease stage. In the remaining 18 children, the initial treatment was chemotherapy. Two of them, who did not respond, underwent laminotomy with symptomatic benefit. One more patient, who had a partial response to chemotherapy, underwent delayed laminectomy to remove residual intraspinal disease and obtained further neurological improvement. No patients was treated with radiation therapy as first or secondary choice.

Twenty-two out of the 26 cases (85%) are alive with a follow-up of 12–55 months (median, 22). The four remaining children died of tumour progression. Neurological response in relation to disease stage and initial treatment are reported in Table 2.

Table 1
Patient characteristics and clinical presentation

Characteristics	Present series		Retrospective study
	N	%	%
Sex			
M/F	11/15	42/58	50/50
Age			
<12 months/≥12 months	12/14	46/54	40/60
Primary tumour site			
Thorax	12	46	37
Abdomen	12	46	55
Pelvis	1	4	7
Other	1	4	1
Stage			
2/3	20	77	71
4/4s	6	23	29
Neurological abnormalities			
Motor deficit grade 1	5	19	57
Motor deficit grade 2	16	61	29
Motor deficit grade 3	5	19	13
Time between neurological symptoms and diagnosis			
<1 week/1–4 weeks	5/10	19/38	17/37
1–2 months/>2 months	3/6	11/23	18/28
Not evaluable	2	8	0
Specific therapy			
Surgery	8	35	31
Chemotherapy	18	65	58
Radiotherapy	0	0	12
Secondary surgery	2	8	0

Table 2
Neurological response in relation to therapy and disease extent

Therapy	Total	Neurological response					
		Complete		Partial		No	
		Localised	Stage 4	Localised	Stage 4	Localised	Stage 4
Chemotherapy	18	7	–	6	2	2	1
Laminotomy	8	1	–	2	2	2	1
Total	26	8	–	8	4	4	2

4.1.3. Long-term sequelae

In our previous study, children treated with chemotherapy only had less orthopaedic sequelae compared to those treated by surgery or radiation therapy. In the present series, out of 14 children with follow-up above 2 years, seven have developed orthopaedic sequelae, including a single instance of scoliosis following laminotomy. More details on these cases are reported later on.

4.1.4. Conclusions

The percentage of children with neuroblastoma and epidural compression in this series is 4.9% (5.2% in the previous publication). In analogy with our previous report, about 50% of patients were younger than one year, and the proportion of thoracic and of localised tumours was higher than in the remaining population. No variation in the time elapsed from onset of symptoms to diagnosis was noted. Our data seem to confirm that chemotherapy is adequate in relieving neurological symptoms in the majority of cases. Neurosurgery was effective in the two cases which did not improve with chemotherapy. Finally, even in the present series a significant number of cases developed neurological and/or orthopaedic sequelae.

4.2. Germany (by Thorsten Simon, Cologne)

4.2.1. Patients and methods

Patients of the Cooperative German trials NB90, NB95 and NB97 with neuroblastoma diagnosed between September 1989 and December 2003, were included in this analysis. For management of symptomatic intraspinal involvement, neurosurgery was strongly recommended. During the last years, the potential of chemotherapy was acknowledged and initial chemotherapy was accepted as an alternative. Radiotherapy was reserved for the management of critically ill patients. Symptomatic transverse myelopathy was defined as presence of paraplegia or impaired motor function of extremities, impaired bladder voiding, or impaired stool control. Complete and incomplete loss of function were distinguished.

4.2.2. Results

The series is made of 1966 patients with median age at diagnosis of 1.3 years (range 0–36). The median observation time was 5.3 years (0.03–16.6). Ninety-three patients (4.7%) presented with clinical symptoms of spinal cord compression at diagnosis. Fourteen of them had paraplegia, and 79 had severely impaired function of legs, bladder and bowel. Children with spinal cord compression were younger than patients without transverse myelopathy (0.73 vs. 1.32 years; $P=.001$), had fewer cases with *MYCN* amplification (6.9 vs. 16.7%; $P=.032$), more localized tumours (74 vs. 52%; $P<.001$), and a far higher proportion with thoracic primary tumour (42% vs. 16%; $P<.001$). The highest frequency of transverse myelopathy was found in stage 3 (Table 3). Details of the presenting symptoms were available in 91/93 patients. Eighty-two presented with motor deficit of the lower extremities, 25 complained of diffuse or localized pain, 13 had bowel incontinence, and 12 bladder dysfunction. The median duration of symptoms prior to diagnosis was 17 days (range 0–495).

Symptomless intraspinal involvement defined as unequivocal presence of tumour tissue in the spinal space without neurological symptoms was found in additional 111 patients. Of note, the proportion of patients with evidence of intraspinal tumour tissue was higher in NB97 (12.9%) compared to NB90 (7.4%), as a consequence of an increased use of MRI instead of CT at diagnosis.

Table 3
Characteristics of 1966 neuroblastoma patients

	Transverse myelopathy		P
	Yes	No	
Patients	93	1873	
Gender			
M/F	45/48	1019/854	
Age			
Mean (years)	.73	1.32	.001
MYCN			
Single copy	67	1287	.032
Amplified	5	259	
Not assessed	21	327	
INSS stage			
1–2–3	69	978	<0.001
4–4s	24	895	
Primary site			
Neck	0	49	<.001
Chest	39	289	
Abdomen	54	1509	
Not detected	0	26	

4.2.3. Treatment

Fifty-two patients (56%) underwent emergency neurosurgery for transverse myelopathy, 41 (44%) received chemotherapy without any preceding surgery. No patient was initially treated with radiotherapy. Thirteen chemotherapy patients underwent neurosurgery after starting chemotherapy. Of 111 patients with asymptomatic intraspinal involvement, 31 underwent neurosurgery.

4.2.4. Outcome

The general 5-year event-free survival was 62±1%, the 5-year overall survival was 72±1%. Compared to other patients, children with initial symptomatic spinal cord compression had a similar 5-year event-free survival (71±1 vs. 61±1%; $P=.6$) but a better 5-year overall survival (85±4 vs. 71±1%; $P=.004$). Separate analysis of localized and stage 4 neuroblastoma echoed these results. In stage 4s no difference was found at all.

Only 1366 patients surviving 2 years or longer were included in the analysis of late effects. Transverse myelopathy was cured without residual symptoms in 47 of 67 patients (Table 4). The duration of symptoms prior to treatment had no impact on the neurological outcome: patients with an history lasting 3 days or less had the same frequency of late myelopathy (3/8 patients) as patients with an history >3 days (17/59; $P=.446$). Increasing the cut-off to 7 days gave similar results ($P=.610$). Patients with complete transverse myelopathy more frequently had residual neurological deficits (6/13=46%) than patients with incomplete transverse myelopathy (14/54=25%). The difference was not significant, possibly because of the small patient numbers ($P=.138$).

There was no clear impact of treatment on long-term neurological outcome: 30 patients started with chemotherapy immediately after the diagnosis was established. Eight of them (27%) presented with residual neurological symptoms during follow-up, compared to 12/37 (32%) who underwent initial neurosurgery ($P=.6$). Among 30 children starting with chemotherapy, 12 had to undergo secondary neurosurgery. The median time interval between the start of chemotherapy and neurosurgery was 122 days (range 2–402). Five of 12 patients (42%) had persisting neurological symptoms, compared to 3/18 (17%) who did not require second line neurosurgery ($P=.14$). The two patients who had early operation performed 2 and 5 days after chemotherapy start had persisting symptoms, whereas 3/10 patients with delayed chemotherapy done 35+ days after chemotherapy start had late neurological impairment.

Scoliosis developed in 39 cases. It was far more common after initial myelopathy (12/67=18%), but it was observed in other patients as well (27/1299=2%; $P<.001$). The proportion of scoliosis was similar among children who underwent neurosurgery for spinal cord compression (8/48=17%), and those who had chemotherapy only (4/19=21%; $P=.46$).

4.2.5. Conclusions

Patients with symptomatic intraspinal involvement by neuroblastoma had a better survival, which might

Table 4
Outcome of 1366 patients surviving >2 years after diagnosis

	Initial transverse myelopathy		P
	Yes	No	
Patients	67	1299	
Residual neurological symptoms			
No	47	1292	<.001
Yes	20	7	
Scoliosis			
No	55	1272	<.001
Yes	12	27	

be explained by their younger age, higher incidence of localized tumours, and lower proportion of *MYCN* amplified tumours. Even when a long time elapsed between first occurrence of symptoms and treatment, complete recovery of neurology was possible and vice versa. The risk of neurological and orthopaedic sequelae appeared to be similar after chemotherapy or neurosurgery as initial treatment. All analyses was limited by the small number of patients.

4.3. Poland (by Walentyna Balwierz, Krakow)

Based on retrospective analysis we present demographics, diagnostic procedures, treatment modalities and results of therapy in patients with neuroblastoma who presented with symptomatic or asymptomatic epidural compression. The observation was finished in December 2003.

4.3.1. Patients demographics

In the years 1997–2003, a total of 185 patients with neuroblastoma were treated in seven centres of the Polish Paediatric Solid Tumours Study Group. Twenty-two patients (12%) had tumour penetrating into the spinal canal at diagnosis.

4.3.2. Symptoms at presentation

Seven/24 patients had no clinical symptoms of epidural compression. Extension of the tumour into the spinal canal was found by radiological imaging in six children and during surgery in one case. In 15 patients (65%), symptoms of epidural compression were present at diagnosis, consisting of paresis in all, sphincteric dysfunction in 10, pain in 4, and sensitivity dysfunction in 2. Most patients had more than one symptom at diagnosis. Paresis with sphincteric dysfunction was the most common presentation. The presence of intraspinal tumour extension was documented by radiological imaging. The median duration of symptoms prior to diagnosis was 1.2 months (range 0.1–4.2).

4.3.3. Treatment

Thirteen children, including nine symptomatic, received chemotherapy as upfront treatment, according to different regimens, depending on patients age and disease extension. Five of these patients had delayed surgery without laminectomy (two with neurological symptoms). Three further patients had delayed laminectomy because of persistent neurological symptoms after chemotherapy. In one of them, infiltration of meninges was found during neurosurgery. In 3/22 children (including two with symptoms), epidural compression was approached by laminectomy as initial treatment. They all received adjuvant chemotherapy according to stage. Six children underwent first upfront surgery on the intrathoracic/abdominal component of the primary tumour and then chemotherapy. None of the patients was treated with radiotherapy as first choice, but three children with symptomatic epidural compression received delayed radiotherapy because of poor response to primary treatment.

4.3.4. Outcome

Fourteen of 22 patients (64%) are alive with no evidence of neuroblastoma, with a follow-up of 5–129 months (median, 45). Two patients are alive with disease. Six children died, including two infants (five from neuroblastoma progression, one from secondary leukaemia). Five-year progression-free survival for infant and non-infant patients is 0.88 and 0.32, respectively. Two of three children with *MYCN* amplification died of disease progression.

4.3.5. Neurological outcome

Five of 15 patients who presented with paresis (including three infants) recovered completely. In eight children (five infants), partial recovery was observed, and in two resolution of symptoms was not obtained.

4.3.6. Complications

No serious complications of laminectomy were observed, except for one case of scoliosis. One asymptomatic child developed Horner's syndrome as a thoracoscopy complication. Leukaemia developed in one infant during the second year of treatment for neuroblastoma.

4.3.7. Conclusions

Due to the small number of patients, variety of treatment modalities employed, and lack of a standardized approach, it is very difficult to evaluate the efficacy of the different therapeutic approaches used. Laminectomy is probably not necessary in most

children with dumbbell neuroblastoma, especially in infants. It is necessary to introduce prospective therapeutic strategies for better disease control. Further improvement of therapeutic strategy for children with neuroblastoma and spinal cord compression calls for association of individual centres in groups which would co-operate in research projects, improving diagnosis and pursuing optimisation of treatment methods.

4.4. United Kingdom (by Joanna Begent, London)

4.4.1. Patients and methods

In order to analyse our experience of neuroblastoma affecting the spinal cord at one UK centre, we conducted a database search followed by retrospective notes analysis. Our aim was to analyse management and outcome of children with stage 2/3 neuroblastoma with spinal involvement treated over a 20-year period, during which 387 children were diagnosed having a neuroblastoma, of whom 115 had stage 2 or 3 disease. We reviewed imaging reports of these 115 children, of whom 22 had evidence of an intraspinal tumour component. Our study looked at 13 girls and 9 boys. The majority of children (72%) presented at <1 year of age (median 0.81, range 0–1.8). Two cases presented at birth. In our cohort, 14 children had stage 3 and 8 had stage 2 disease. Time from first symptoms to presentation varied from 24 h to 3 months (median, 15 days). Eight patients had had over 3 weeks of symptoms prior to presentation. Some of the patients were international transfers. The tumours were spread between sites with nine of the 22 having thoracic and 7/22 having pelvic tumours; the remaining six were lumbar tumours. At presentation all were symptomatic although only 15/22 had neurological symptoms. Eleven children had primarily limb neurology, seven of these had flaccid paralysis; four had bladder/bowel symptoms and seven had non-neurological symptoms—from incidental abdominal masses to a cough. The incidence of sphincteric dysfunction at diagnosis is possibly underestimated, in reason of the fact that most of the patients were infants. None of the patients reported pain or sensitivity disturbances. No child had amplification of the *MYCN* gene in his tumour.

4.4.2. Therapy and results

Treatment strategies varied, although all children had at least two therapeutic modalities. At presentation, three symptomatic children underwent neurosurgery, with partial recovery. Twelve children were treated with chemotherapy first: 9 (75%) had a partial, and 3 (25%) a complete neurological recovery. Five patients also received steroids. In four children, in which chemotherapy did not succeed in relieving neurological symptoms, neurosurgery was performed and it leads to an improvement in three of them (75%). Laminectomy was performed in five cases and laminoplasty in two more recent operations. Fifteen children underwent surgery on the intra thoracic/abdominal component of the primary tumour alone. Twenty-one had chemotherapy from varying protocols (mostly carboplatin/etoposide, or OPEC/OJEC). Two children received radiotherapy as an adjunct to other treatment (16–20 Grey, respectively). There is a wide follow-up interval in our cohort (1–20 years; mean 9.3); all but one of these patients are alive (one patient died from other causes). Overall survival from disease is 100%; however, 50% of children have serious sequelae and only six have none. Six patients cannot walk, all of whom presented with limb neurology. Two are paraplegic, one of whom had a congenital tumour. Five are paraparetic, including the second congenital case. Two of these had laminectomy at diagnosis. Twelve have ongoing urinary incontinence and/or bowel control problems, including the two congenital cases. Ten children have spinal deformity; this group includes 7 of the 15 who did not have spinal surgery and three of the seven who did. Two children have subsequently had corrective surgery (one post-laminectomy). Other problems include two children with significant foot size differences, three with altered sensation in their legs and two suffering with erectile problems. Both children who presented with congenital spinal cord neuroblastoma are severely disabled. All the other non-ambulant children had over 2 weeks of limb neurology prior to presentation. Two of the four were referred from outside the UK. Four of the six children with no long-term sequelae had a history lasting less than a week.

4.4.3. Conclusions

In summary, in our study 19% of children with stage 2/3 neuroblastoma have spinal involvement.

Management of these children has not been consistent, however, prompt treatment clearly improves neurological outcome. Although prognosis from disease is good, long-term morbidity remains high.

4.5. Children oncology group (by Sue Cohn, Howard Katzenstein, and Wendy London; Chicago, Atlanta, and Gainesville, USA)

4.5.1. Patient demographics

Between May 1990 and January 1998, 83 children with intraspinal neuroblastoma were registered on POG NB Biology Protocol #9047 [11]. The age at diagnosis ranged from birth to 13 years and 2 months (median, 10 months). Eight patients had stage A tumours; 23 had stage B disease; 28 had stage C; 21 had stage D; and one patient had stage DS disease. The primary intraspinal component was located in the thoracic region in 55 (66%) of the 83 patients. The estimated survival rate $\pm$standard error of the entire group at 5 years was $71 \pm 9\%$.

4.5.2. Symptoms at presentation and initial treatment

Forty-three patients had neurological symptoms at diagnosis; 15 patients had severe neurological deficits with paraplegia, five had moderate symptoms consisting of paresis with bowel and/or bladder dysfunction, and 22 had mild deficits with paresis alone. Sixty-six patients received upfront chemotherapy; eight received initial radiotherapy; 23 underwent primary laminectomy; 31 underwent upfront surgical resection without laminectomy, and 25 did not undergo an initial surgical resection.

4.5.3. Neurological outcome

Six of the 15 patients who presented with paralysis completely recovered neurological function; two following surgical decompression with laminectomy, one following chemotherapy, and three following chemotherapy and radiotherapy. In this cohort, the length of time between the development of symptoms and the initiation of therapy was inversely correlated with the degree of neurological recovery. Two of five patients with moderate neurological deficits completely recovered neurological function; one following laminectomy and one following chemotherapy. Seventeen of 22 evaluable children with mild symptoms fully recovered; eight following laminectomy, one following surgical resection without laminectomy and eight following treatment with chemotherapy. No clear correlation between the development of symptoms and the initiation of therapy was seen in the moderately or mildly affected patients. Five of 40 patients who did not have neurological symptoms at the time of diagnosis acquired neurological symptoms following treatment; three developed Horner's syndrome, one parasthesia, and one paralysis following a delayed surgical resection.

4.5.4. Orthopaedic late effects

A total of eight patients (10%) in our series were noted to develop scoliosis. Scoliosis was considered to be severe in one case (curvature $>40°$); three were categorized as moderate curvature (>20 and $<40°$); and four were classified as mild ($<20°$). Seven of the eight patients with documented scoliosis had undergone an initial laminectomy.

4.5.5. Conclusions

The less severe the presenting neurological deficits, the more likely patients are to have a complete recovery. The rate of neurological recovery was similar for patients treated with chemotherapy compared to those managed with surgical decompression and laminectomy. Fewer orthopaedic sequelae were seen in the children managed with chemotherapy than were observed in children managed with laminectomy.

4.6. Memorial Sloan-Kettering cancer Center (by Kim Kramer, New York, USA)

We recently reviewed the cases of epidural neuroblastoma using neurological outcome and spinal deformities as endpoints [12]. From 1987 to 1998, 46 children with neuroblastoma invading one or more neural foramen by MR or CT with or without myelography were identified. Children were 7 weeks—18 years of age (median 3 years). Twenty-four patients (52%) were male. Two-thirds of patients had high-risk stage 4 disease by INSS criteria; the remainder 15 had loco-regional disease. Among 32 patients in whom epidural disease was discovered at initial presentation, the majority of tumours were of primary retroperitoneal origin, with a smaller percentage from the thoracic or pelvic region. Presenting signs or symptoms among the 46 patients included

pain (20 cases), weakness or gait disturbance (14), incontinence (3), sensory abnormalities (3), scoliosis (1) or were asymptomatic (13). Some patients had more than one symptom.

4.6.1. Therapy

A sole surgical approach was primarily reserved for patients with asymptomatic loco-regional disease; symptomatic patients with loco-regional disease were treated either by surgery or combination chemotherapy. Combination chemotherapy was favoured for patients with metastatic disease; those with stage 4 disease with associated neurological deficits were treated with both chemotherapy, chemotherapy and radiotherapy, and surgical decompression.

4.6.2. Neurological outcome

All patients with loco-regional neuroblastoma who were initially treated with surgery remained stable or improved neurologically. Five of six patients with stage 4 disease with associated neurological deficits treated surgically remained stable or improved; one paraplegic patient did not improve. Twelve stage 4 patients with neurological deficits were treated with chemotherapy, or chemotherapy and radiation therapy; nine remained stable or improved and three had neurological deterioration requiring emergent neurosurgery; all three subsequently improved.

4.6.3. Spinal deformities

Overall, 11/46 patients (24%) were noted to have spinal deformities (scoliosis and/or kyphosis) at some point (median, follow-up 5 years). Spinal deformities were rare in patients treated non-surgically (2/16). Age at diagnosis and median follow-up periods did not differ in patients who developed spinal deformities vs. those who did not.

4.6.4. Conclusions

Our experience shows that in patients with pre-existing neurological deficits, surgical intervention successfully stabilises or improves the neurological condition. Some stage 4 patients with neurological deficits may be treated with chemotherapy initially, but approximately 25% have progressive neurological deficits eventually requiring surgical intervention. Spinal deformity is a common late event in patients with epidural neuroblastoma, and is more frequently observed in patients treated with neurosurgical intervention (30%) compared to those treated with chemotherapy alone (12%). Low-risk neuroblastoma patients with epidural extension may be offered surgery alone, but the risk of scoliosis must be weighed against those of cytotoxic chemotherapy.

4.7. Japan (by Tomoko Iehara, Kyoto)

Children less than 12-month-old, presenting with neuroblastoma and spinal cord compression between June 1994 and May 2004, were enrolled into the Japanese prospective studies #9405 and #9805 [13]. Patients were treated with a conservative approach, avoiding neurosurgery, and prospectively followed-up. The aim of the study was to assess the efficacy of this treatment.

4.7.1. Patient demographics

Six hundred and fifty-seven cases of neuroblastoma were diagnosed in the study period. Thirty-three of them (5%) presented a dumbbell tumour. Twenty-two cases (67%) were detected by mass screening and 11 (33%) had symptoms. Nineteen patients were male, 14 female. Median age at diagnosis was 7 months. The primary tumour site was the thorax in 17 patients, abdomen in 14 and pelvis in 2. Three cases had stage 1, 10 had stage 2A, 2 had stage 2B, 12 had stage 3 and 6 had stage 4. None of the patients had *MYCN* oncogene amplification over 10 copies.

4.7.2. Symptoms and treatment

Nine patients had neurological symptoms at presentation, consisting of paraparesis in five cases (associated to sphincteric dysfunction in two), Bernard–Horner syndrome (CBHs) and dyspnea in three cases, CBHs and arm paresis in one case. No patients underwent neurosurgery. All symptomatic children were treated with chemotherapy. One patient received irradiation to the thoracic vertebrae. Patients with localized resectable disease underwent tumour excision (15 cases). Among them, stage 3 patients received post-operative chemotherapy (10 cases). Patients with localized unresectable tumours (12 cases) or stage 4 disease (six cases) underwent pre-operative chemotherapy. Fourteen of them also received post-surgery chemotherapy.

4.7.3. Outcome

No patients had neurological worsening. Complete neurological recovery was observed in two cases, and partial recovery in four. One patient, who had multiple malformations, died of disease. Five patients relapsed, but achieved a second remission. Twelve patients are alive with residual disease at 1–101 months of follow-up (median, 37). Twenty patients are alive with no evidence of disease (10–108 months; median, 65). Event-free survival of patients treated with surgery alone is 89%, of patients with localized disease who received post-operative chemotherapy is 80% and of patients with unresectable tumours or stage 4 disease, who underwent pre-operative chemotherapy is 80%.

4.7.4. Conclusions

The prognosis of infants with dumbbell-type neuroblastoma is good. Local control can be achieved without neurosurgery. A treatment plan without laminectomy can be considered adequate.

4.8. France (by Dominique Plantaz, Grenoble)

In 1990, a prospective study concerning children with localised neuroblastoma presenting with spinal cord compression was opened [14]. All these cases were treated with chemotherapy, in an attempt at reducing morbidity of laminectomy, while maintaining a good survival rate and offering the best chances of neurological recovery. Both symptomatic and asymptomatic patients were included into the study. Chemotherapy was administered according to NBL 90 and NBL 94 protocols. Decompressive neurosurgery was performed at diagnosis only in cases of initial severe and rapidly progressing neurological deficit. Patients enrolled into the NBL 90 protocol, but not those enrolled into NBL 94 protocol, underwent secondary laminotomy to remove intraspinal residue when appropriated.

4.8.1. Demographics

From 1990 to 1999, 618 cases of neuroblastoma were diagnosed. Seventy-eight of them (12.6%) had intraspinal extension. The median age at diagnosis was 8 months. Fifty-nine percent of the dumbbell patients were less than 12 months old, compared to 44% of non-dumbbell cases ($P=.04$). The proportion of thoracic tumours was significantly higher among dumbbell patients (45 vs. 24%; $P=.01$) and *MYCN* gene amplification was significantly less frequent (one of 57 cases in which *MYCN* status was studied, vs. 38 of 390; $P=.02$).

4.8.2. Results

Forty-four patients (56%) had some degree of neurological impairment, scored as partial in 24 patients (30%) and severe in 20 (26%). Thirty-eight of 44 patients (86%) were initially treated with chemotherapy. Of them, 24 (63%) had a complete and 8 (21%) had a partial neurological recovery, in 5 (13%) chemotherapy failed to improve the neurological status and one patient worsened. Intraspinal tumour regression was evaluated in 63 patients, both symptomatic and asymptomatic. Complete regression of the intraspinal tumour was observed in 50% of cases, while in 37% partial regression was described and in 11% no tumour shrinkage was noticed. Only in one case the intraspinal tumour progressed despite chemotherapy. Six symptomatic (14%) and two asymptomatic patients underwent primary neurosurgery. Only one of them was enrolled into the NBL 94 protocol. Fifty percent of symptomatic patients completely recovered, 33% partially improved and in one case surgery failed to improve patient's status. Thirteen patients, 10 of whom enrolled into NBL90 protocol, underwent secondary neurosurgery, for tumour residue (11 cases), worsening (1), or intraspinal relapse (1). Overall and event-free survival of dumbbell patients was comparable to non-dumbbell cases. The presence of an intraspinal residue did not correlate with risk of relapse. Forty-three of 44 symptomatic patients were evaluated for late sequelae. Seven cases (16%) presented mild, and 10 (23%) presented severe neurological sequelae (inability to walk and/or bowel/bladder dysfunction). Ten patients (23%) suffer from severe orthopaedic sequelae.

4.8.3. Conclusions

In France, initial laminectomy has become an uncommon procedure. Delayed laminotomy to remove an intraspinal residue after chemotherapy and extraspinal surgery has been performed, but can probably be avoided, without risk of jeopardizing the excellent survival of these patients. Although the diagnosis tends to be made earlier than in the past, antenatal or long lasting spinal cord compression still put about 25% of symptomatic patients at risk of life-long sequelae.

Table 5
Late sequelae

Type of sequelae	Cases		Neurological impairment		Treatment			
			Moderate	Severe	Laminotomy		Chemotherapy	
	#	%	#	#	#	%	#	%
Bladder dysfunction	12	52	5	7	10	67	2	25
Scoliosis	9	39	6	3	8	53	1	12
Orthesis	9	39	1	8	7	47	2	25
Reduced functional independence	8	40	2	6	7	47	1	12

Summary of the Italian experience.

5. Late effects (by Paola Angelini, Genova)

We have reviewed the Italian patients observed between 1979 and 2002. Patients were re-examined by MRI, orthopaedic, neurological, urologic and oncologic evaluations. The WeeFIM™ instrument was used to score the patients' functional independence. Both patients and parents were requested to separately answer a modified PedsQL™ questionnaire, adapted for children (6–12 years) and adolescents (13–18 years). Twenty-three patients, 13 male, 10 female, median age at diagnosis 8 months (range, 1–83), were evaluated. Twenty had a localized tumour, two had stage 4 and one had stage 4s disease. Motor impairment at diagnosis was mild in one case, moderate in 15, and severe in 7. Neurosurgery was the first therapeutic approach in 15 cases, chemotherapy in 8. Median follow-up was 7 years (range, 2–22). Table 5 summarises the results of our combined evaluation, with particular regard to bladder function, scoliosis, need for orthesis to walk, and age-adjusted functional independence. Six patients needed surgical correction of limb deformities, related to Achilles' tendon in two cases, hip in two, knee and feet in one case each. Eight patients had feet deformities. All patients answered the quality of life questionnaire. Parents tended to underweight some issues, mostly social and emotional. Anger and tiredness were the most commonly reported feelings. All patients described future, sometimes ambitious projects.

Overall, in 85% of patients relevant sequelae were documented, as a consequence of either epidural compression, or of its treatment. However, having more compromised patients been easier to contact and evaluate, an overestimation of the incidence and severity of sequelae might have occurred. The ascertainment of a correlation between presence and/or severity of sequelae and type of treatment, or severity of neurological impairment at diagnosis was difficult, as more severely affected patients received more aggressive treatment, often including laminectomy. The prospective collection of standardized and comprehensive data on larger series is warranted.

6. Conclusions (by Bruno De Bernardi, Genova, and Howard Katzenstein, Atlanta)

Symptomatic epidural compression in a child with a tumour is a medical emergency since severe sequelae may follow if the condition is not timely re-cognised and treated. Neuroblastoma is by far the tumour that most frequently present with such clinical pattern. A proportion of these cases despite a positive MRI have no symptoms arising the question if they require specific treatment. No doubt instead, that children with positive MRI and neurological symptoms do require prompt multidisciplinary attention. The contribution brought to this Workshop clearly shows that a number of disagreements still exist for a variety of aspects. In the conclusive part of this review, the controversies concerning these aspects will be summarised.

6.1. Definition

For sake of accuracy, the term spinal cord compression should be limited to the cases for whom the compression occurs just over the spinal

cord. However, in a proportion of the cases the compression involves the nerves and/or the cauda equina, without affecting the medulla. As a matter of fact, the clinical aspects, the neurological compromise and the eventual late effects may considerably differ in the two situations, being commonly less severe in the latter. The term epidural compression should therefore be preferable. In this review, the authors are have been free to use the term of their preference. In the future, an unified terminology will be desirable.

6.2. Incidence

Although it varies considerably in the different published series as well in the presentations of this Workshop, the incidence of cord compresssion seems progressively decreasing, possibly as an effect of early diagnosis. However, it has to be noted that some of these children receive chemotherapy on an emergency basis before a histologic diagnosis, making them ineligible for more recent trials. On the opposite, the inclusion of asymptomatic cases may definitely increase the incidence. Achieving an agreement on this issue appears of particular importance to compare different series of patients.

6.3. Clinical presentation

In analogy to previous series, children included in this review had more frequently localised disease, younger age and thoracic location. Since all these features are known to be associated with better outcome, not surprisingly children with epidural compression have a higher chance of survive than the general neuroblastoma population.

6.4. Definition of neurological deficit

Surprisingly, the description of neurological deficits in the various series lacks of common terms making it difficult to compare them for both clinical presentation, response to therapy and late results.

6.5. Imaging of epidural compression

MRI is definitely the instrument of choice to document the involvement of intravertebral foramina and spinal canal. However, it has still to be made clear if the presence of either involvement documented by MRI should not be sufficient to authorise the initiation of specific therapy in absence of neurological symptoms. The tendency emerged in the Workshop has been negative to this regard.

6.6. Time elapsed between symptoms and treatment

It is commonly believed that a long interval between first evidence of epidural compression and initiation of specific therapy is associated with worse clinical response and greater risk of relevant late sequelae. The data presented in this Workshop are uneven and controversial at this respect.

6.7. Therapeutic approach

Dexamethazone is often immediately administered but its benefit is controversial. Significant disagreement persist regarding the optimal specific therapeutic approach. While some consider that any case of documented epidural compression (even asymptomatic) should undergo a neurosurgical operation, others state the opposite. The presentations of this Workshop clearly document this noticeably different behaviour. Well organised prospective studies are needed to seriously face and solve this important issue.

6.8. Late effects

A large proportion of children with neuroblastoma presenting with epidural compression will develop significant sequelae, which may be especially severe in case of primary or secondary grade 3 neurological deficit (paraplegia) [15]. Once again, one is surprised of the scarcity of publications at this respect and lack of guidelines to follow to optimally treat these children in order to minimise the eventual sequelae.

6.9. Perspectives

The main aim of this Workshop was to collect on a large scale data on clinical and therapeutic aspects of epidural compression in neuroblastoma, this has allowed to document that a variety of aspects are not well defined and therefore require clarification. The participants have agreed on the necessity of planning an additional Workshop to fix common guidelines.

6.10. Rationale for an international neuroblastoma cord compression registry

Over the past two decades, uniform criteria for staging neuroblastoma have been developed (INSS), and discussions are ongoing to develop to uniform international neuroblastoma risk-group (INRG) criteria. The international neuroblastoma community has long recognized that a universal language is needed to compare results of clinical trials that are conducted in the various cooperative groups and countries throughout the world to insure that treatment strategies are optimised. As evidenced by this mini-review, the management of spinal cord compression in neuroblastoma remains controversial. Reviews of published series from largely describe retrospectively collected data, and to date, there are no uniform criteria for defining the type or severity of the neurological deficits that are associated with cord compression. In addition, criteria for evaluating neurological response to therapy are lacking. A better understanding of neuroblastoma and cord compression could be obtained through an international registry. Such a registry would allow for the prospective collection of data and would provide a uniform language to describe the neurological symptoms of these patients. As evidenced by the important contributions of the other international neuroblastoma collaborations, the creation of an International Neuroblastoma Cord Compression (INCC) Registry would facilitate the collection of a complete and uniform set of data which would hopefully lead to the development of an evidence-based approach to this problem.

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報　告

神経芽腫

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1　はじめに

神経芽細胞腫は，神経提由来の腫瘍で，小児固形悪性腫瘍の中では多い腫瘍の一つである．また，この腫瘍は，小児がんの中でも腫瘍特性が最も多様性を示すがんとして知られ，その治療は，リスク分類に従って選択されるのが一般的である．診断は病理で神経芽腫と確定するか，尿中のvanillylmandelic acid (VMA)，homovanillic acid (HVA) の上昇と骨髄で神経芽腫を示唆する細胞塊を検出することによってなされる．治療方針決定には，正確な病理診断と生物学的特性によるリスク分類が必要で，手術的摘出または生検での腫瘍の解析が必須となる．リスク分類は，診断時年齢，組織分類（嶋田分類，INPC分類：International Neuroblastoma Pathology Classification）[1-3]，病期（INSS分類:International Neuroblastoma Staging System），*MYCN* 遺伝子増幅，腫瘍細胞の染色体数（Ploidy），等の分子生物学的因子を組合わせて判定する．通常では，高リスク群，中等度リスク群，低リスク群に分類して，治療方針を決定する．こうした状況で，手術不能の進行がんは，生検後にリスク判定を行い，それに応じた化学療法を行い，そののちに摘出術を行う．

2　組織学的分類

神経芽腫群腫瘍の組織分類は，従来の日本小児外科学会悪性腫瘍分類では，良性の神経節腫と，悪性は神経節細胞の混在の有無による神経節芽腫と神経芽腫に分類し，前者は高分化型，混在型，低分化型に，後者は花冠細繊維型と円形細胞型に亜分類していた．嶋田らは，年齢によって分化傾向を示すことに着目し，年齢因子を加味した病理所見からのリスク分類として嶋田分類を提唱した．この考え方がベースとなり，今は，International Neuroblastoma Pathology Classification (INPC) Systemが提唱されており，これに基づいて分類する（表1）[1-4]．

3　病期分類とリスク分類

病期は，従来，Evansの分類[5]に従い，I，II，III，IV期とIV-S期に分類されていたが，本邦の日本小児外科学会悪性腫瘍分類[6]では病期IV期をIV-A期とIV-B期（IV-S期と同じ転移部位であるが，原発巣が進行しているもの）に分けていた．最近は，手術による切除範囲を加味したINSS分類[7,8]で分類されることが多い．

リスク分類は，表3に示した様に，診断時年齢，病期（INSS分類：International Neuroblastoma Staging System），組織分類（嶋田分類，INPC分類：International Neuroblastoma Pathology Classification）[1-3]，*MYCN* 遺伝子増幅，腫瘍細胞の染色体数（Ploidy），等の因子を組合わせて判定する[9]．通常では，高リスク群，中等度リスク群，低リスク群に分類するのが一般的であるが，表4に示した一番染色体短腕（1p）欠失，17番染色体長腕増加，Trk A発現などのマーカーで3群（タイプ1から3）に分けられている腫瘍特性からみたサブセット分類を参考に決定する[10-12]．

4　治療法の概要

低リスク症例の治療は，ほとんどの症例は外科

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的摘出のみであるが，一部の症例に 6-12 週の化学療法を付加する．脊髄の圧迫症状，病期 4S で肝腫大のために呼吸障害がある症例などである．薬剤毒性を起こさないように各薬剤の投与総量を最小限にする．中等度リスク群では，外科切除後に 12-72 週の化学療法を行うのが原則である．腹部の神経芽細胞腫で腎臓を巻き込んだ症例に対して，化学療法前に腎臓合併切除は行うべきでない[14]．（エビデンスのレベル：III，勧告のグレード：B）．高リスク群では，大量の cisplatin や ifosfamide などを用いた大量多剤併用化学療法を行い，その後に外科切除を行い，さらにその後に全身照射，造血幹細胞移植などの治療法を組合わせた化学療法を行う．放射線療法はこうした化学療法前，施行中，終了後に組合わせる．終了後，分化誘導療法を行うことがある[15]．一部では，大量化学療法，放射線療法を施行し，最後に局所療法として手術を行うことが試みられているが，治

表 1　International Neuroblastoma Pathology Classification (Shimada System) [1, 2].

以下の４グループとそれぞれの亜分類に分ける

1. Neuroblastoma (Schwannian, stroma-poor)
   - a. Undifferentiated
   - b. Poorly differentiated
   - c. Differentiating
2. Ganglioneuroblastoma, Intermixed (Schwannian stroma-rich, GNB stroma-rich, mature Schwannian cell > 50%)
3. Ganglioneuroma (stromal dominant)
   - a. Maturing (scattered neuroblasts, not in nests)
   - b. Mature ganglio-neuromatous tumour with a few randomly dispersed immature neuroblasts. No distinct nests of neuroblasts are found.
4. Ganglioneuroblastoma, Nodular

Unfavorable histology group は以下のように定義する:

1. All undifferentiated neuroblastomas
2. All nodular ganglioneuroblastomas
3. All neuroblastomas in patients older than 5 yrs of age
4. Poorly differentiated / differentiated neuroblastomas with high MKI in patients less than 1.5 yrs
5. Poorly differentiated neuroblastomas with low MKI or differentiated neuroblastomas with high/intermediate MKI's in patients 1.5-5 yrs

表 2　INSS 病期分類[7, 8]

Stage 1	原発部位に限局した腫瘍：肉眼的完全切除で，組織学的腫瘍残存は問わない．ただし，腫瘍に接して切除されたリンパ節は転移があってもよい．
Stage 2A	限局性の腫瘍で肉眼的にも不完全切除；組織学的に腫瘍に接していない同側のリンパ節転移を認めない．
Stage 2B	限局性の腫瘍で完全または不完全切除．同即の腫瘍に接していないリンパ節転移あり．組織学的に対側のリンパ節転移を認めない．
Stage 3	切除不能の片側性腫瘍が正中線を越えたもの（局所リンパ節転移はありまたはなし）．または片側性腫瘍で対側の局所リンパ節転移があるもの．
Stage 4	原発腫瘍の進展範囲に問わず，遠隔リンパ節，骨，骨髄，肝，皮膚，さらに／または他の臓器に進展するもの（stage 4S を除く）
Stage 4S	限局性の原発腫瘍（stage 1, 2A, 2B）で，転移部位が皮膚，肝，骨髄にとどまるもの．ただし，年齢は 1 歳未満． 骨髄転移は浸潤腫瘍細胞が有核細胞の 10％未満．

療成績は明らかでない．（エビデンスのレベル：IV，勧告のグレード：D）

放射線療法は，化学療法に反応せず生命危機あるいは臓器障害をきたす症状がある時，中等度リスク群で化学療法と手術にて治療が不十分の時，および高リスク群に施行する．高リスク群では，全摘後の局所照射が行われる場合もある．

脊髄圧迫症状で緊急の対処を要する場合，化学療法，放射線療法，椎弓切除術がある．椎弓切除術は側彎という晩期障害をきたす．脊髄圧迫症状が出現して72時間以上を経ると非可逆性の神経障害を残すので，緊急椎弓切除は72時間以内症例に限定される．低リスク群あるいは中等度リスク群では，晩期障害が少ない化学療法が選択され

表3　神経芽細胞腫のリスク分類[9)]

INSS病期分類	診断時年齢*	MYCN増幅	INPC病理分類	DNA ploidy	リスク分類
1	—	—	—	—	低
2A/2B	1才未満	—	—	—	低
	1才以上	なし	—	—	低
		あり	favorable	—	
		あり	unfavorable	—	高
3	1才未満	なし	—	—	中等度
		あり	—	—	高
	1才以上	なし	favorable	—	中等度
			unfavorable	—	高
		あり	—	—	高
4	1才未満	なし	—	—	中等度
		あり	—	—	高
	1才以上	問わない	—	—	高
4S	1才未満	なし	favorable	hyperdiploid	低
			—	diploid	中等度
			unfavorable	—	中等度
		あり	—	—	高

＊診断時年齢においても，1才半で分けるべきであるとの報告[10)]もある．
—：結果を問わない項目

表4　神経芽細胞腫の生物学的因子によるサブセット分類[11-13)]

生物学的因子	タイプ1（低悪性度）	タイプ2（悪性度中等度）	タイプ3（高悪性度）
MYCN 増幅	なし	なし	あり
核型	hyperdipolid	near-diploid	near-diploid
	near-triploid	near-tetraploid	near-tetraploid
1p 欠失	稀	少数	あり
17q 増加	稀	あり	あり
Trk A 発現	高発現	低発現／なし	低発現／なし
Ha-ras 発現	高発現	低発現／なし	低発現／なし
テロメラーゼ	低発現／なし	低発現	高発現
年齢	通常1才未満	通常1才以上	1　5才
INSS 病期分類	1，2，4S	3，4	3，4
無病3年生存	90%以上	30-50%	20%以下

ることがある.

マスクリーニングで発見された乳児例などでは,手術による合併症を避ける目的で,外科的な処置による確定的な組織診断なく経過観察される場合がある[16,17]. 米国では,周産期のEvansの病期分類Iでこのような試みがなされている.

(エビデンスのレベル:IV,勧告のグレード:D)

5 化学療法ガイドライン

A) 低リスク神経芽腫

外科的に全摘できた低リスク症例に対する化学療法:

低リスク群の治癒(長期生存)率は90%以上であることから[18-22],外科的摘出術のみにて経過観察する[18,20-22]. (エビデンスのレベル:I,勧告のグレード:A)

外科的に全摘できた低リスク症例で,化学療法施行による有意な成績向上が得られた報告はない.以下の症例が対象となる.

1) INSS 2の低リスク腫瘍で50%以上の腫瘍が残存した症例
2) INSS 2の低リスク腫瘍で,術後なお生命危機や臓器障害をきたすおそれがある症例.臓器障害には呼吸障害,腎障害,脊髄圧迫症状,消化管閉塞,尿路閉塞や凝固障害などがある[23,24]. (エビデンスのレベル:III,勧告のグレード:B)

化学療法の期間は6-24週間,cisplatin, cyclophosphamide, doxorubicin, etoposide, vincristineを副作用予防のため比較的低濃度で使用する. vincristineとcyclophosphamideを一週毎に投与して,3クール後の効果を判定し,必要な場合さらに3クールを追加する. Carboplatinまたはcyclophosphamideまたはcyclophosphamideとdoxorubicin1回とetoposideを3回/3日間, carboplatin, cyclophosphamide, doxorubicinを各1回のレジメンを3週ごと6-24週行う.

化学療法が奏功しない症例には放射線療法を併用する場合もある[23]. これらの薬剤を低リスク腫瘍に使用した群と使用しない群での長期生存率の有意差は得られていない[20]. (エビデンスのレベル:IV,勧告のグレード:D)

病期4Sの症例の治療は,臨床症状によって異なる. このタイプの腫瘍は臨床的に安定していれば治療は不要である. 生後2-3ヶ月未満児に多い巨大な肝腫大による心肺や大血管の圧迫などの合併症は治療対象となる[25-27]. 80例の病期4S症例の長期生存率は,保存的治療例が100%であったのに対し,低用量の化学療法を受けた症例は81%であった. 原発巣の切除は治癒(長期生存)率の改善につながらない. (エビデンスのレベル:II・勧告のグレード:B)[22].

B) 中等度リスク群の化学療法

中等度リスク群の化学療法の対象は

1) 1歳未満の*MYCN*遺伝子増幅がないINSS3・4期の症例
2) 1歳以上で*MYCN*遺伝子増幅がなくINSS3期でINPC(嶋田)分類favorable typeの症例,
3) 1歳未満のINSS4S期で*MYCN*遺伝子増幅がなく,INPC(嶋田)分類unfavorable typeかdiploid核型など予後不良因子を持つ症例である.

薬剤の組み合わせとコースは,cyclophosphamide, vincristine, pirarubicin, cisplatin(持続静注)を組み合わせた5日間のレジメンとcyclophosphamideとDTICからなる5日間のレジメンを組みあわせて4週毎に52-76週まで行う.

INSS3症例の化学療法は欧米ではcyclophosphamide, etoposide, doxorubicin, cisplatinを組み合わせたレジメンを3-4週ごとに行い,18週で手術を行った後,化学療法,放射線療法施行し,維持療法としてcyclophosphamide; doxorubicin, cisplatin + etoposideを交互に4回繰り返し,最後に残存腫瘍の手術を行うプロトコールと,先の4剤を4週ごとに行い,12週で骨髄を採取し,17週で手術,化学療法と放射線療法後に自家骨髄移植を行うプロトコールが用いられている. 移植後は維持療法を行うが,13シスレチノイン酸による分化誘導療法を組み合わせることもある[18].

また，最近は，carboplatin，cyclophosphamide，doxorubicin，etoposide を組み合わせてたレジメンも試みられている．予後不良因子を有する症例では，各薬剤の投与量と投与回数を増量させる．治療期間については，favorable type では 12 週，unfavorable type では 24 週行う．1 才未満で MYCN 遺伝子増幅がない INSS 4 期の症例は中等度リスク群であるが，favorable histology で triploid であれば，化学療法は 12 週，それ以外は 24 週とする．favorable type の中等度リスク群における放射線療法は，腫瘍によって生命または臓器が侵される場合に限り施行する．unfavorable type における放射線療法は，24 週の化学療法後や，second look 手術後の遺残腫瘍に対して行う．

治療成績は概して，50-70％の長期生存が期待できるが，1 歳未満の方が治療成績が良い傾向にある[28-31]．（エビデンスのレベル：III，勧告のグレード：B）嶋田分類や INPC 分類で unfavorable type であったり，*MYCN* 遺伝子が増幅している症例の長期生存は 50％と悪い[13, 22, 32]（エビデンスのレベル：II，勧告のグレード：A）．特に，INSS4 期症例の長期生存率は，診断時年齢に大きく左右される．1 才未満の症例は長期生存が期待できるが，その期待率は生物学的特性により異なり，*MYCN* 遺伝子が増幅のない症例の治癒率は 90％以上であるのに対し，*MYCN* 増幅例は 10％前後と不良である[33]（エビデンスのレベル：II，勧告のグレード：A）．米国で乳児神経芽腫の切除不能例または遠隔転移例を核 DNA 量から diploid と hyperdiploid の二群に分けて治療し，前者の 3 年生存率は 55％に対し，後者は治療を減弱したにも関わらず 94％であり，予後因子による層別化の必要性を示した．（エビデンスのレベル：III，勧告のグレード：C）さらに，マススクリーニング発見例では，1 歳未満の *MYCN* 遺伝子増幅がない INSS3 期症例は，化学療法を施行しない群と施行した群で長期生存率に差がないとの報告がある[33-34]（エビデンスのレベル：IV，勧告のグレード：C）

薬剤毒性予防のため，それぞれの薬剤の総投与量を低く保つことが肝要である．実際には，先に示した stage III の神経芽腫患児に対する大量化学療法＋骨髄移植では，228 人中治療毒性は，重篤な腎障害，心筋障害，聴力障害などは，5％以下で，4 人が治療関連死したが，全員 1 歳以上で 2 人は原疾患の増悪によるものであった[7]．また，110 人の転移性乳児神経芽腫患児のスタディでは，死亡した 16 人中 13 人が原疾患の再発で死亡し[23]，治療毒性は，さほど高くない．（エビデンスのレベル：III，勧告のグレード：C）

C）高リスク群の化学療法

高リスク群の化学療法の対象は

1) INSS1 期または 2A/2B 期で *MYCN* 増幅症例
2) 1 才未満の INSS 3/4 期で *MYCN* 増幅例
3) 1 才以上の INSS 3 期で嶋田 unfavorable histology，*MYCN* 増幅のいずれか一方を有する症例
4) 1 才以上の INSS 4 期例，1 才未満で INSS 4S 期かつ *MYCN* 増幅のある症例[35]

標準的な化学療法は，cyclophosphamide，cisplatin，doxorubicin，トポイソメラーゼ II 阻害剤が 34-45％の奏効率を示したとの報告[36]などから，これらの薬剤が併用療法の基軸となっている．実際には，cisplatin，または carboplatin を中心に，cyclophosphamide，ifosfamide，vincristine，doxorubicin（または類似薬剤），etoposide（または類似薬剤）などを様々な用量で組合わせたレジメンが用いられ，4 剤以上を併用した 4-5 日程度のレジメンの寛解導入率は 76-93％である[38, 39]．これらのレジメンは 4 週ごとに繰り返され，2－5 クール後に化学療法に反応した後に，原発巣を second look 手術で切除し，その後に大量化学療法と自家幹細胞移植（骨髄移植あるいは末梢血幹細胞移植）を行う．大量化学療法は，melphalan，etopside，carboplatin の組み合わせによる HiMEC レジメンが主流である．自家骨髄移植を施行した群と化学療法のみの治療群の 2 群のランダム比較試験で，自家骨髄移植例での長期生存率の向上が得られている[7, 40]．しかし，これらのスタディで全身放射線照射（TBI）併用と併用しな

いレジメンが使用されており，TBIの有用性やリスクについてのエビデンスは示されていない．最近では，TBIを用いないレジメンの自家移植の有効性が示唆されている．また，自家移植にパージングした骨髄を用いた方が良いかどうかの結論は得られていない．原発巣の完全摘除ができなかった症例では原発部位への放射線療法を考慮する．転移巣への放射線療法は症例により決定すべきである[41]．（エビデンスのレベル:IV，勧告のグレード:D）自家移植から回復後に，13-シスレチノイン酸の経口投与を6ヶ月間行うこともある．自家幹細胞移植後に13-シスレチノイン酸の経口投与を6ヶ月間投与の有効性が報告されている[7]（エビデンスのレベル：II，勧告のグレード：B）

本邦では，cisplatin，cyclophosphamide，vincristine，pirarubicinの5日間のレジメンを中心に，cyclophosphamideとDTIC，cyclophosphamideとpirarubicinとcarboplatin，ifosfamideとetoposideの3レジメンを組み合わせたプロトコールで治療し，*MYCN* 増幅例にはそれ以外と異なる高用量のレジメンを使用してきた．その結果，*MYCN* 遺伝子の増幅のない例の5年生存率は34.4%に対し，*MYCN* 増幅例は33.3%であり[38]，臨床評価を得ている．同様に *MYCN* 増幅を伴った症例が *MYCN* 増幅のない症例に比べ予後不良と考えられていたが[41, 42]，高用量の化学療法で差がないとの報告もある．[43]（エビデンスのレベル：IV，勧告のグレード：D）

一般の治療成績として，高リスク群の症例の長期生存率は10-40%で，強力な治療を行っても晩期再発や治療終了後5年以上での死亡例も報告されている[44, 45]．（エビデンスのレベル：II，勧告のグレード：A）

高用量化学療法に自家骨髄移植を施行した群と3クールの地固め療法を追加した群の比較では，大量化学療法＋移植群で3年無病生存率（ＥＦＳ）は34.4%と化学療法群の22.4%よりも有意に高い．さらに，その後に6ヶ月の13-シスレチノイン酸投与を追加した症例の 3年ＥＦＳはより良好であった[7, 46]．（エビデンスのレベル：II，勧告のグレード：B）

転移を伴う高リスク群の症例に対し診断時に完全な外科切除を行うことの利点は明確にされていない[34, 47]．（エビデンスのレベル：IV，勧告のグレード：C）

診断時の原発巣の完全摘除が長期生存率を改善したとの報告があるが，広範切除よりも切除率を左右している腫瘍の特性に依存した結果とも考えられる[48-52]．（エビデンスのレベル：IV・勧告のグレード：D）

高リスク群で中心薬剤となるCisplatinでは，消化器症状（悪心・嘔吐，食欲不振等）がほとんど全例に起こる．また，急性腎不全等の腎障害，骨髄機能抑制，ショック（アナフィラキシー様症状），聴力低下，難聴，耳鳴，うっ血乳頭，球後視神経炎，皮質盲，脳梗塞，うっ血性心不全，まれに溶血性貧血，血栓性微小血管症，心筋梗塞，精神症状，肝障害が現れることがある．なお，フロセミドによる強制利尿を行う場合は腎障害，聴器障害が増強されることがあるので，輸液等による水分補給を十分行う．Cyclophosphamideは用量依存性に抗腫瘍効果が得られるが，大量使用時の副作用として出血性膀胱炎が知られており，その発症予防のためにメスナの使用が一般的である．さらに，腎毒性，性腺機能障害についても注意が必要である．また，Doxorubicinに特徴的である心毒性は5-10%程度の患者に出現しているが，患者に対する総投与量を最大500mg/m^{2}に限定することにより，ある程度回避しうるものと期待できる．ただし，この心毒性は若年患者にはより高頻度に出現するというデータがある[53]ため，特に乳児患者においては総投与量をさらに減じて考慮するべきであると考えられる．また，胸部や腹部に放射線治療を受けた患者も心毒性のリスクが高いため，同様の考慮が必要である．Etoposideを含む併用化学療法による重大な晩期障害として，二次がん特に二次性白血病と骨髄異形成症候群がある．本腫瘍の化学療法は，併用療法で使用するために，骨髄抑制やその他の副作用が増強される可能性があるが，G-CSF製剤投与や輸血などの支持療法を積極的に行うことで対処が可能である．

また，高リスク神経芽腫に対する化学療法とし

て，大量化学療法＋骨髄移植療法が行われ，大量化学療法＋移植群の3年無病生存率が化学療法群よりも高かったが，血液学的な治療毒性は，初期治療中にgrade3，4を71%に認めた．治療関連死は移植群と化学療法群では6%と3%で有意な差は認めなかった[11]．一方，同様の治療方針であり，転移性神経芽腫に大量化学療法と自家造血幹細胞移植が行われ，7年の無増悪生存率は29%で，造血幹細胞移植を受けた患者29例中の毒性死亡は4名（13%），全てが造血幹細胞移植の時期に発生しており，骨髄移植による副作用の有無については結論が出ていない[37]．（エビデンスのレベル：III，勧告のグレード：D）

現在，GM-CSFとモノクローナル抗体療法，131 I-MIBG（metaiodobenzylguanidine）によるターゲット放射線療法，複数回の幹細胞移植を伴う大量化学療法，幹細胞移植前の131 I-MIBG療法などが試みられている54?61)．また，131Iでラベルした神経芽腫細胞に対する抗体（抗GD2抗体）療法を導入したプロトコールも進行中で，観察期間の中央値が19ヶ月ながら24例中18例が非進行で生存中である62)．（エビデンスのレベル：IV，勧告のグレード：D）

D）再発神経芽細胞腫（セカンドライン）の治療

再発或いは進行神経芽細胞腫の長期生存率とそれらの対する治療は，診断時の病期，再発時の腫瘍特性，再発部位とその程度，初期治療等多くの因子によって異なる．広範な再発時には，さらに集中的な治療を行っても通常予後不良である[63, 64]．一部に，再手術が奏功する症例がある．cyclophosphamideとtopotecanの併用療法[50]やirinotecanの投与が再発例に試みられている[65-69]．

低リスク群腫瘍の治療後の再発腫瘍に対しては，外科的切除が可能であれば切除し，その後同様の化学療法レジメンを12週，残存する場合，あるいは転移巣がみられた場合は24週行うことが試されているが，まだその有効性は検証されていない．

中枢神経系への浸潤が5-10%に認められる．稀に脳髄膜転移，脳内転移がみられる．神経学的症状の改善には早期発見と治療が肝要である[70, 71]．（エビデンスのレベル：III・勧告のグレード：B）

低リスク腫瘍として治療された症例の再発例は，中等量のcisplatin，cyclophosphamide，doxorubicin，etoposideによる化学療法を行う．副作用防止のため，各薬剤の総投与量は低く抑えるべきである．年長児で嶋田のunfavorable histologyあるいはMYCN増幅を伴って再発した症例は，高リスク群に準じて治療を行う．

転移再発症例のうち，診断時がINSS1，2，または4Sで，1才以下での再発であれば，腫瘍の特性に準じて治療を行う．明らかに予後良好な特性で，4S症例の転移部位で，3ヶ月以内の再発は経過観察とする[25]．（エビデンスのレベル：III・勧告のグレード：B）

3ヶ月以後の再発あるいは4Sの転移部位以外の転移では，原発巣を可能な限り切除し，12-24週の化学療法を行う[34]．（エビデンスのレベル：III，勧告のグレード：B）

INPC（嶋田）分類のunfavorable histologyあるいはdiploid核型が再発，転移巣に認められれば24週の化学療法を行う[72]．（エビデンスのレベル：III，勧告のグレード：C）

中等度リスク症例として治療した患者の局所再発では，化学療法終了後3ヶ月以上経て，表1，2に示した様な各因子で予後良好特性を示す再発巣は外科的に切除する．完全に切除できなかった時は，さらに12週の化学療法を追加する．化学療法はcisplatin，cyclophosphamide，doxorubicin，etoposideを使用し，各薬剤の総投与量は副作用予防のため低く維持すべきである．

転移再発のうち，化学療法終了後3ヶ月以内の再発，あるいは予後不良特性を有している場合は高リスク群に準じた治療を選択する．しばしば，ifosfamideと高用量cisplatin併用が用いられる．幹細胞移植や13-シスレチノイン酸の化学療法後の投与は生存期間を改善させる可能性がある[18]．

高リスク症例の再発は極めて難治であり，予後不良である[54]．新薬の治験等の考慮も必要かもしれない．

E）終わりに

小児悪性腫瘍の化学療法においては，長期無病生存を期待しうる高い有効性を期待できるが故に，成人の化学療法に比較してより強力に行われる傾向にある．このため，予想しうる副作用に十分な支持療法を行ったとしても，重篤な出血や敗血症をはじめとした重症感染症などを合併する危険が回避出来ない場合があり，合併症死に至る症例が少数ながら存在する．よって，本剤を用いた併用療法を行う場合においては小児悪性腫瘍に対するがん化学療法を熟知している専門的な小児腫瘍専門医師が使用する，もしくは専門医師の監督下において使用されるべきである．

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